Sessions of Acupuncture and Nutritional Therapy Evaluation for Atrial Fibrillation (Santé-AF): a feasibility study

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia globally, associated with increased risk of stroke, debilitating symptoms and a decrease in health-related quality of life (HRQoL). Current treatments for AF may not provide symptomatic relief, and are associated with risks and adverse responses that may decrease HRQoL. A systematic review was conducted, revealing a small amount of low-quality evidence demonstrating positive effects of complementary therapies for symptoms and HRQoL in AF. This suggests that a large-scale trial would be justified to investigate whether complementary therapies may improve symptoms and/or HRQoL in AF. To decrease the uncertainty associated with a future trial, a feasibility study was carried out.

Thirty participants were recruited to a three-arm parallel-group pragmatic randomised controlled trial of acupuncture and nutritional therapy compared with usual care. Seven feasibility objectives (comprising a total 10 domains) were investigated quantitatively and qualitatively, including participants' willingness to take part, appropriateness of eligibility criteria, participant retention, and acceptability of interventions and study assessments. Additional parameters were investigated relating to practitioners, and the effect of the COVID-19 pandemic. The study used a convergent mixed methods design to understand not only whether, but why, objectives and domains were (in)feasible.

A future large-scale trial was found to be feasible. Of the 10 feasibility domains, six were feasible without modification, one required process-related modifications to achieve feasibility, and one was re-analysed to correct participant error, thus achieving feasibility. Two domains were abandoned as inappropriate/unviable but did not affect feasibility. Recommendations made to improve feasibility across all domains included changes in eligibility criteria to reflect real-world populations, and changes in study assessments to attenuate participant burden. The study also proposed an extension to pragmatic trials methodology – the inclusion of nested case studies/series – to give a fuller representation of the effects of complementary therapies.

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Declaration

I declare that this thesis is a presentation of original work and I am the sole author.

This work has not previously been presented for an award at this, or any other, University.

All sources are acknowledged as references.

No publications have arisen from this thesis to date.

1 Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia with debilitating symptoms including breathlessness, palpitations and tachycardia, dizziness, fatigue and depression (Li et al., 2022a; Hindricks et al., 2020); the condition is associated with a sharp decrease in health-related quality of life (HRQoL) (Jones et al., 2020; Dalteg et al., 2016). Because AF risk increases with age, disease burdens are commensurate with an ageing population globally, and the burden on healthcare systems is likewise substantial: in the UK, it is estimated that AF will account for up to 4.27% of total National Health Service (NHS) expenditure by 2040 (Burdett and Lip, 2022). AF is also strongly associated with increased morbidity; a recent study found that a typical newly-diagnosed AF patient has an average of up to five comorbid conditions (Chamberlain et al., 2017), thought to result from pathophysiological mechanisms shared between AF and conditions such as chronic obstructive pulmonary disease (COPD), heart failure and diabetes. These collectively contribute to remodelling of the cardiac substrate and worsening cardiomyopathy, which increases the risk of stroke (Escudero-Martínez, Morales-Caba and Segura, 2023; Ronsoni et al., 2021). Current treatments include medications such as beta-blockers and anti-arrhythmics; refractory AF is treated using procedures such as electrical cardioversion (in which a controlled electrical shock is delivered to the heart) or ablation (which uses a catheter to isolate pulmonary veins and remove portions of the pathogenic cardiac substrate). Treatments are not always successful in achieving normal sinus rhythm (NSR), with a high proportion of patients reverting to AF within a year of treatment (Brandes et al., 2020; Russo et al., 2021).

There is increasing interest in the potential of complementary therapies to attenuate symptoms and/or increase quality of life in AF (Lei et al., 2021; Abdul-Aziz et al., 2018; Kanmanthareddy et al., 2015; Brenyo and Aktas, 2014). Complementary therapies, operating on a holistic principle of "treating the patient, not the disease" (Birch, 2019a), may lend themselves to working with the complex interlocking comorbidities of the typical AF patient. In general, therapies are safe when performed by qualified practitioners (Pratt et al., 2020), with minimal undesired side-effects of the types associated with conventional AF treatment. Complementary therapies may also promote self-efficacy and a change in lifestyle behaviours that contribute to AF severity (Pinto et al., 2022; Wenham et al., 2018). In addition, the effects of complementary therapies have been shown to persist longitudinally (Vickers et al., 2018; Thomas et al., 2006), which may offer longer-term cost-utility.

This thesis is an account of the Sessions of Acupuncture and Nutritional Therapy Evaluation for Atrial Fibrillation (Santé-AF) feasibility study. The study took the form of a three-arm parallel group pragmatic randomised controlled trial, designed to reduce the uncertainties of a future large-scale

trial investigating the effectiveness of two complementary therapies (acupuncture and nutritional therapy) when used adjunctively with usual care for symptoms and HRQoL in people with atrial fibrillation.

Background (**Chapter 2**) describes the condition of atrial fibrillation (AF) and its impact on individuals and health systems, as described in the literature. Current treatments are critically discussed, and the potential for complementary therapies to attenuate symptoms and improve HRQoL in AF is outlined. A rationale is given for a systematic review to synthesise the current evidence for complementary therapies in relation to symptoms and HRQoL in AF.

A **Systematic review** (**Chapter 3**) synthesises the current evidence. Ten studies were included, covering four therapies. All were assessed at high or "some concerns" risk of bias, and exhibited a high degree of clinical and methodological heterogeneity such that neither statistical synthesis nor assessment of the certainty of evidence was advisable. The chapter draws together the rationale for a future trial and for this feasibility study, and sets out the feasibility study's research question, aim, and the objectives that structure the investigation.

Methodology (**Chapter 4**) discusses and justifies the methodological approaches of the feasibility study as a pragmatic trial of two complex interventions. Current guidance on complex interventions is discussed, using acupuncture and NT as illustrative examples, and evaluating the choice of mixed methods and pragmatic trial design in this context. Finally, the philosophical foundations of Santé-AF's various methodologies are summarised and justified.

Methods (**Chapter 5**) outlines the methods used in the feasibility study, including adaptations made during the COVID-19 pandemic, and justified in relation to the research question. Quantitative criteria specifying thresholds for progression to a future trial ("progression criteria") are devised and justified.

Results (**Chapter 6**) presents the findings of the feasibility study, and applies the progression criteria to each objective. General findings are also presented (i.e., those not specific to the feasibility objectives but of interest to a future trial) and a quantitative determination of overall feasibility is made.

In **Discussion and Recommendations** (**Chapter 7**), the outcomes of feasibility assessment are critically discussed, bringing together quantitative and qualitative data to reach a more nuanced understanding of the study's design in relation to the population and interventions investigated. A number of recommendations are made to increase a future trial's operational feasibility, and also to increase the reliability and real-world generalisability of a future trial's results. Benefits and harms of the interventions are critically considered, and the limitations and biases of the feasibility study are discussed.

The **Conclusion** (**Chapter 8**) draws together a brief summary of the findings and the recommendations for a future trial; considers the strengths and weaknesses of this study; makes recommendations for future research; and concludes with a statement answering the study's research question.

2 Background

This chapter will set out the condition of atrial fibrillation (AF) and its impact on individuals and health systems, as described in the current literature. Pathophysiological mechanisms are discussed, together with a brief look at emergent research into the underlying condition of atrial myopathy, which may account for some of the pathophysiological mechanisms linking AF with an increased risk of stroke. Current treatments for AF are discussed, together with their associated benefits and risks. A rationale is presented for the investigation of complementary therapies in relation to AF, and the chapter concludes by drawing together the rationale for a systematic review to synthesise the current evidence for complementary therapies for symptoms and HRQoL in AF.

2.1 Atrial fibrillation: a summary

Atrial fibrillation (AF) is the most common cardiac rhythm disturbance globally (Li et al., 2022a; Lippi, Sanchis-Gomar and Cervellin, 2021; Di Carlo et al., 2019; Chugh et al., 2014). Its prevalence in the UK is rising across all age groups and both sexes (Adderley et al., 2019). It is associated with substantially increased morbidity and mortality (Benjamin et al., 2019) and therefore represents a significant burden to healthcare delivery systems and national economies, and to individual patients (Holmlund et al., 2022; Jiang et al., 2022; Tito and Borghetti, 2021).

2.1.1 Pathophysiology

AF is a supraventricular tachy-arrhythmia in which the heart's electrical signals are not, as in normal sinus rhythm (NSR), propagated via the sino-atrial node, but instead generated from the entire atrial area. This results in uncoordinated atrial activity and inefficient emptying of the ventricles. Typical AF symptoms include palpitations/tachycardia, dizziness, fatigue, breathlessness, chest pain, syncope, inability to tolerate exercise, disordered sleep and depression (Hindricks et al., 2020; Wynn et al., 2014).

2.1.2 Types of AF

AF is classified as one of three types, defined by episode characteristics (National Institute for Health and Care Excellence, 2023):

- **Paroxysmal**: episode length of 30 seconds to seven days, where periods of AF are succeeded by periods of normal sinus rhythm (NSR) (known as spontaneous cardioversion);

- **Persistent**: episodes longer than seven days that may be cardioverted to NSR with pharmacology or procedures;
- **Permanent**: where pharmacology or procedures fail to cardiovert, or recur within 24 hours; or longer-standing AF where intervention is not attempted or indicated (this is a decision to attempt no further treatment).

2.1.2.i Other types of AF

AF of any classification may be asymptomatic (formerly known as "silent"): population studies suggest a prevalence of 10-40% of the population with asymptomatic AF (Ballatore et al., 2019; Turakhia et al., 2018; Boriani et al., 2015).

A proportion of patients with new-onset AF may spontaneously convert to NSR and need no further treatment ("transient AF") (January et al., 2019; Kirchhof et al., 2016). This was demonstrated in the RACE 7 ACWAS trial, which used a "wait and see" approach to cardioversion: for 69.0% of 218 participants in a delayed cardioversion group, conversion to sinus rhythm occurred spontaneously within 48 hours (Pluymaekers et al., 2019).

2.1.3 Epidemiology

With an ageing population worldwide, global AF prevalence stands at its highest ever (Lippi, Sanchis-Gomar and Cervellin, 2021). Analysis of data from the Global Burden of Disease study in 2019 estimated 59.7m people with AF worldwide, an increase of 103.9% since 1990 (Li et al., 2022a). A study focused on the European Union estimated 8.8 million cases in adults older than 55 in 2010 (95%CI=6.5–12.3m) and projected that this would double by 2060 to 17.9m (95%CI=13.6–23.7m) (Krijthe et al., 2013). Di Carlo et al. (2019) added to this projection with an estimate that in the EU population aged 80+ years in 2060, AF prevalence will reach 65.2%.

Public Health England (PHE) estimated the 2019 prevalence of AF in the English population as 2.5% (95%CI=2.4–2.5) or 1.5m people (Public Health England, 2020). However, these figures are likely to be an overestimate as they were not corrected for England's ethnically diverse population, which is associated with lower AF prevalence (Ugowe, Jackson and Thomas, 2018). Also, as Robson points out (2020), the Swedish reference study used by PHE to estimate English prevalence included all cases of AF, including transient and perioperative episodes, which may lead to overestimation by as much as 100% when applied to some geographic areas of England.

2.1.4 Clinical outcomes

The concept of "AF begets AF" – the increase in AF thought to support progressive atrial remodelling and eventual atrial fibrosis (Nattel, 2017; Saksena et al., 2007), which in turn increases

AF severity – underlies the concept of disease progression in AF, from paroxysmal to persistent to permanent (Rivner et al., 2020; Calkins et al., 2018). Progression is thought to be associated with an increased risk of adverse events including stroke or embolism (adjusted HR 2.2 (95%CI=1.1–4.0) (Ogawa et al., 2018) and all-cause mortality (adjusted HR 1.77 (95%CI=1.1–2.9)) (Vitolo et al., 2023). Progression has also been linked with decrease in HRQoL due to increase in symptomaticity and associated adverse effects (Dudink et al., 2018), particularly when associated with multimorbidity (Bamgbade et al., 2020). Nguyen et al. (2023) estimated that 5.5% of patients may progress each year, while a cross-sectional study of the Euro Heart Survey put the figure at an average of 5.2 per 100 patient-years (Blum et al., 2019). Both studies noted specific risk factors or comorbidities that were predictive of progression, including biomarkers of coagulation, inflammation, atherosclerosis, and modifiable risk factors such as BMI and systolic blood pressure. Asymptomatic AF is thought to carry the same outcome risks as symptomatic AF for all-cause mortality, cardiovascular death or thromboembolic events/stroke (Sgreccia et al., 2021; Healey et al., 2012).

New evidence continues to emerge of associations between a wide range of adverse outcomes and the presence of AF. Odutayo et al.'s meta-analysis of cohort studies (2016) identified RRs between 4.9 and 1.3 for a range of outcomes in the presence of AF, including all-cause mortality, major cardiovascular events, ischaemic heart disease, heart failure, chronic kidney disease and peripheral arterial disease. Since then, individual observational studies and meta-analyses have continued to link AF with elevated risks of, amongst others, all-cause mortality (standardised mortality rate 3.7 (95%CI=3.6–3.8)) (Lee et al., 2018); kidney disease (HR 1.4 (95%CI=1.3–1.5)) (Chen et al., 2022); myocardial infarction (RR 1.5 (95%CI=1.3–1.9)) (Ruddox et al., 2017) and cognitive impairment (HR 1.4 (95%CI=1.3–1.5)) (Koh et al., 2022).

2.1.4.i AF, stroke and atrial myopathy

AF has long been established as an independent risk factor for stroke, thought to be implicated in 1 in 4 of all ischaemic strokes (Ding et al., 2023), and with a five-fold increase in risk of all types of stroke historically thought to arise from pooling of blood in the atria and left atrial appendage, causing clots which in turn cause emboli (Wolf, Abbott and Kannel, 1991). More recent research has cast doubt on this model. Firstly, stroke rates in the context of AF are declining over time despite increasing prevalence of AF (Schnabel et al., 2015); secondly, the RACE series of trials found that patients continue to sustain stroke irrespective of both anticoagulation status and AF severity (Kirchhof et al., 2023; Crijns and Van Gelder, 2020; Van Gelder et al., 2017). This has challenged the traditionally theorised pathophysiological mechanisms, and weakened the causal link thought to exist between AF and stroke (Christiansen et al., 2016). In turn, the broad strategy of AF therapeutics has begun to shift, now placing less emphasis on anticoagulation for stroke

prophylaxis than on treating the patient's comorbidities – known as the "look beyond the ECG, treat the patient" approach (De With et al., 2019; Alings et al., 2013).

Recent research has begun to hypothesise that the condition of atrial myopathy, also known as cardiomyopathy, cardiac myopathy or atrial cardiopathy, may function as a stronger causal factor in stroke than AF (Ronsoni et al., 2021; Sajeev et al., 2020; Ahmad et al., 2020; Shen, Arora and Jalife, 2019). Several investigators have proposed a complex causal model in which a combination of systemic pathologies (particularly vascular pathologies such as endothelial dysfunction or atrial fibrosis), together with increasing age, length of diagnosis, and a range of genetic factors and comorbidities such as autonomic disruption, hypertension, diabetes and heart failure that may exacerbate these pathologies, cumulatively contribute to the development of atrial myopathy (Saleeb-Mousa et al., 2023; Goette et al., 2016). The condition affects atrial structure and function, leading to cardiac substrate remodelling, and may therefore in turn contribute directly and indirectly to AF incidence, progression and adverse clinical outcomes including stroke (Escudero-Martínez, Morales-Caba and Segura, 2023; Nso et al., 2021; Rivner et al., 2020; D'Souza, Butcher and Buck, 2018; Kamel et al., 2016):

> AF is often a progressive disorder… its progression is related to the degree of atrial myopathy that is present… atrial myopathy is a consequence of the effects of underlying comorbidities as well as the effect of AF itself (tachycardic effects on the atria)… adverse outcomes can be a consequence of AF, the underlying atrial myopathy, as well as direct consequences of any comorbidities present (Reiffel, 2023).

The hypothesis requires further investigation, but early speculations suggest that therapeutically targeting atrial myopathy may decrease AF occurrence and severity (Rivner et al., 2020), and may also decrease stroke risk; it may also explain why current treatments for AF appear to have variable rates of success (**2.1.8 below**). In providing a possible explanation for the observed disjuncture between AF severity and stroke, underlying atrial myopathy may also account for the commonly observed phenomenon of younger, healthier patients who register increased AF symptomaticity compared with older patients with more comorbidities but less awareness of AF (Charlesworth and Palumbo, 2023). Santé-AF's consultant cardiologist commented:

> Young, healthy people feel their AF really badly but actually don't seem to have more strokes compared to the older people who don't feel the AF but do seem to have much higher risk of stroke. [That may be because] the young healthy people have strong atria… if they suddenly lose atrial function for whatever reason, they really feel it. On the other hand, the older patients have already lost atrial function long before… so when they go into AF they don't really feel any different because their bodies have adapted to the loss of atrial function over time (Gupta, 2021)

2.1.5 Risk factors and comorbidities

The current literature on AF investigates a complex web of risk factors for, and comorbidities with, incident AF; the risk of adverse outcomes in the presence of AF with or without risk factors and comorbidities; and the associations and/or causal links between all. In acknowledgement of this complexity, more recent editions of AF guidelines increasingly tend to refer to risk factors and comorbidities as a portmanteau term, and to describe both the upstream and downstream features of health conditions/lifestyle choices occurring concomitantly with AF. This approach avoids any attempt to disentangle factors that may be causative from those that may exacerbate AF, those that result from AF, or those that may simply be associated – or any combination of these (Lip, 2023; Hindricks et al., 2020; Andrade et al., 2020; Brieger et al., 2018; Joung et al., 2018; Naser et al., 2017); it may have helped to pave the way for the newly emergent theories on the pathophysiology of atrial myopathy described above.

People with AF rarely have one risk factor or comorbidity in isolation (Lip, 2023; LaMori et al., 2012). According to Staerk et al.'s study of risk factors, "many people often have a mixture of borderline or elevated levels of risk factors" (2018, p.1): a typical person newly-diagnosed with AF has an average of five comorbid conditions, whether diagnosed or undiagnosed (Chamberlain et al., 2017), and requires multidisciplinary support (Lee et al., 2023). Summing up this complexity, Ramadeen and Dorian observe that "AF is not a single disease, but rather an electrophysiological manifestation of multiple pathologies, complicated by the consequences of the fibrillation itself" (2011, p.1032).

2.1.5.i Risk factors for incident AF

The risk of developing AF has been shown to increase with age, and also with male sex and genetic predisposition (Benjamin et al., 2019; Weng et al., 2018; Allan et al., 2017; Balta et al., 2013). As discussed above, the number of concomitant comorbidities is strongly associated with incident AF: the current European Society of Cardiology (ESC) guideline (Hindricks et al., 2020) identifies a further 16 health-related risk factors for incident AF, of which the most researched are vascular diseases, coronary artery disease, lipid profile, obstructive sleep apnoea (OSA), chronic obstructive pulmonary disease (COPD), diabetes, hypertension, heart failure, metabolic syndrome and inflammatory diseases (Aune et al., 2023; Zakynthinos et al., 2023; Groenewegen et al., 2022; Nicoli et al., 2022; Sagris, Harrison and Lip, 2022; Linz et al., 2021; O'Keefe et al., 2021; Kamil et al., 2020; Seyed Ahmadi et al., 2020; Park et al., 2018; Proietti et al., 2016a; Vanbeselaere et al., 2016). Additionally, four lifestyle factors have been found to represent strong risks for incident AF: physical inactivity, alcohol consumption, smoking and obesity (Díaz-Gutiérrez et al., 2023; Frederiksen et al., 2023; Foy et al., 2018; Ortiz and Kwo, 2015).

Around 140 genetic loci have been associated with incident AF (Kim, Chelu and Li, 2021; Feghaly et al., 2018); although this research field is at an early stage with regard to AF, results are highly suggestive (Zhang et al., 2023). Genetic factors are also thought to play a role in the development of atrial myopathy, with a consequent contribution to remodelling and incidence/progression of AF (Andersen, Andreasen and Olesen, 2021).

Socioeconomic/sociodemographic factors are increasingly seen as risk factors for incident AF (Essien et al., 2021), although the mechanisms are poorly understood. For instance, it is well-established that underrepresented racial and ethnic groups demonstrate a higher incidence of established risk factors, but a lower actual prevalence of AF (Heckbert et al., 2020; Nanda and Kabra, 2019; Ugowe, Jackson and Thomas, 2018; Gillott et al., 2016); epigenetic research is currently attempting to establish the mechanisms of this relationship (Roberts et al., 2016). Similarly, while there is strong evidence of an inverse relationship between a range of socioeconomic markers and risk of incident AF (Lunde et al., 2020; Guhl et al., 2019; Mou et al., 2018; Soliman et al., 2017), higher SES appears counterintuitively to be either not, or only weakly, associated with the lifetime risk of AF when accounting for competing risk of death (Mou et al., 2018; Ataklte et al., 2022). This apparent contradiction may be attributable to the substantial increase in AF risk after 80 years of age: individuals with lower SES have higher rates of mortality and so, in the words of Ataklte et al., “may not live long enough to develop AF” (p6).

Risk factors play a complex role in determining the risk of developing AF (Garg et al., 2020; Neefs et al., 2019; Allan et al., 2017; Naser et al., 2017). It has been shown that multiple risk factors may not exert a simple additive effect: in a 2018 analysis of three generations of the Framingham Heart Study, Staerk et al. found that, in individuals with optimal levels of alcohol consumption, BMI, blood pressure, smoking, diabetes and history of heart failure or heart attack, the lifetime risk of AF was 23.4% (95%CI=12.8-34.5), but this rose to 37.8% (95%CI=33.1–42.4) in individuals with even a single elevated risk factor. In common with many other studies investigating the role of multiple risk factors, Staerk et al. do not include socioeconomic and sociodemographic factors as covariates; there is a need for more studies controlling for multiple risk factors, including socioeconomic and sociodemographic factors, to fully understand these effects.

2.1.5.ii Modifiable risk factors

A number of risk factors are considered modifiable, and with them, their impact on risk of incident AF and risk of AF-related clinical outcomes (Middeldorp et al., 2020; Wingerter et al., 2020; Wong et al., 2020; Hong and Glover, 2018).

Modifiable risk factors divide into two types: firstly, lifestyle/behavioural factors such as physical inactivity, alcohol consumption, smoking and obesity (Frederiksen et al., 2023; Mehta et al., 2021;

Zia et al., 2021; Neefs et al., 2019; Voskoboinik et al., 2019; Di Benedetto et al., 2018; Nalliah, Sanders and Kalman, 2018; Yang et al., 2017); and secondly, those that are amenable to medication, such as hypertension, OSA, diabetes and hyperlipidaemia (O'Keefe et al., 2021; De With et al., 2019; Rienstra et al., 2018; Lau et al., 2017; Yang et al., 2017).

An increasingly strong body of evidence shows the associations between modifiable risk factors, particularly behavioural factors, and the prevention of AF (Tu et al., 2023; Gallagher et al., 2021; Mehta et al., 2021; Chung et al., 2020; Lau et al., 2017). Therapeutic research is also beginning to show that lifestyle and behavioural change targeting modifiable risk factors may attenuate existing AF symptoms and improve HRQoL (AbuElkhair et al., 2023; Seo and Lee, 2023; Middeldorp et al., 2020; Bittman et al., 2022; Nalliah, Sanders and Kalman, 2018; Gallagher et al., 2016). However, AF patients report poor education and information from healthcare providers regarding AF and self-care, which may affect self-efficacy, self-care and ultimately HRQoL (Toscos et al., 2020).

2.1.5.iii Risk factors and adverse outcomes in AF

Once AF is diagnosed, the presence of comorbidities/risk factors is strongly and positively associated with increased risk of adverse outcomes (Foster et al., 2022; Krisai et al., 2020; Jeong et al., 2014). Investigating all-cause mortality, the UK Biobank cohort study found that, adjusting for age, sex, deprivation, anticoagulant status and smoking status, participants with AF had six times the risk of mortality compared with participants with AF but with no comorbidities (Jani et al., 2018). These observational findings were supported in the findings of the ROCKET-AF trial: in AF patients with kidney dysfunction, COPD, peripheral vascular disease, diabetes, heart failure or prior stroke, mortality was significantly increased irrespective of anticoagulation status, and multiple comorbidities were also associated with correspondingly higher mortality (Pokorney et al., 2016).

Some comorbidities/risk factors, including obesity, diabetes, hypertension, metabolic syndrome, OSA and heart failure, are thought to predict recurrence of AF following treatments such as ablation and electrical cardioversion (Han et al., 2022; Glover et al., 2019; Vitali et al., 2018; Mohanty et al., 2014). By contrast, a recent umbrella review of 31 meta-analyses of recurrence predictors following ablation found convincing evidence for only hypertension and metabolic syndrome, and suggestive evidence for depression, as predictors of recurrence (Charitakis et al., 2023).

2.1.6 Impact of AF

2.1.6.i Impact on individuals

Much research on AF focuses on its electrophysiological and therapeutic aspects, with far fewer investigations focusing on psychological and societal aspects (Herrmann-Lingen and Wachter,

2021; Ladwig et al., 2020). Both quantitative and qualitative investigations indicate a range of mainly negative experience, of which the most frequently cited dimensions are symptom severity, HRQoL and emotional distress (a compound term describing any permutation of anxiety, depression, AF-related stress, and/or fear of AF episode onset). These dimensions may be associated with aspects of the condition including diagnosis and treatment, living with AF, and managing AF.

People with AF are, in general, more likely to experience lower HRQoL than people without the condition (Freeman et al., 2015) or people with other cardiovascular diseases (Jones et al., 2020; Aliot et al., 2014). This is linked to multiple factors including medication side-effects and bleeding risk, preoccupation with symptoms, AF progression, fear of future adverse outcomes, difficulties in obtaining effective treatment, the presence of comorbidities whether symptomatic or not, and anxiety regarding AF symptom recurrence (Koutoukidis et al., 2020; Krisai et al., 2020; Potpara et al., 2020; Dudink et al., 2018; Dorian and Angaran, 2017; Rush et al., 2017; Randolph et al., 2016; Altiok, Yilmaz and Rencüso, 2015; Lane et al., 2015). People with AF often perceive a diminishment of health and vitality, which is strongly associated with lower HRQoL (Dalteg et al., 2016). Physical self-image is negatively affected, and people with AF may limit their social and physical activity as a result, leading to increased social isolation and higher incidence of emotional distress (Holmlund et al., 2022). Exercise capacity is reduced, as is tolerance for everyday activities such as climbing stairs (Taylor et al., 2018; Altiok, Yilmaz and Rencüso, 2015; Hoegh et al., 2015), and working hours may be curtailed, leading to financial concerns (Mohanty and Natale, 2021).

Positive influences on HRQoL in AF include anticoagulation status, optimal symptom management and cardioversion following successful treatment (Gabilondo et al., 2021; Varona et al., 2020; Rush et al., 2017; Tan et al., 2018; Raine et al., 2015; Bulková et al., 2014). However, successful treatments are not uniformly associated with improvements in HRQoL, perhaps due in part to the persistence of comorbidities (Mohanty and Natale, 2021); supporting this, it has been shown that attenuation of comorbidities increases HRQoL in people with AF even when AF persists (De With et al., 2019).

Emotional distress levels are higher in AF populations than in healthy equivalents. People with AF experience higher rates of depression and anxiety, and a greater severity of both (Polikandrioti et al., 2018; Kupper et al., 2013; Schnabel et al., 2013), with a greater propensity to develop anxiety disorders (Serpytis et al., 2018) and suicidal ideation (Walters et al., 2018). People with AF also experience anxiety regarding the clinical outcomes of AF, particularly mortality (Aliot et al., 2010): Ekblad et al. found that even when patients had been well-informed regarding AF's direct effect on mortality, "bodily symptoms of AF led to feelings of existential anxiety" (2013, p.135). Anxiety may also arise from unpredictability in symptom onset, which is reported as more challenging than the

actual symptoms (Holmlund et al., 2022; Penela Maceda and Berruezo, 2019). As AF progresses or severity increases, emotional distress increases correspondingly (Gisi et al., 2020; von Eisenhart Rothe et al., 2014).

In AF patients, both HRQoL and emotional distress are repeatedly shown to be associated with symptoms (Abu et al., 2022; Taylor et al., 2022; Jones et al., 2020; Krisai et al., 2020; Son et al., 2019; Witassek et al., 2019; Ekblad et al., 2013). Recent observational cross-sectional studies have nuanced the associations by adjusting for covariates including risk factors/comorbidities (including emotional distress) in addition to standard demographic covariates. For instance, Sadlonova et al. (2022) found no independent association between AF symptom severity and HRQoL when controlling for age, sex and type of AF (the standard covariates), but found a strong association between HRQoL and AF-concomitant diabetes, sleep disturbance, financial stress and generalised cardiac anxiety. Charitakis et al. (2017) found that anxiety, depression and low-grade inflammation were predictive of higher self-reported AF severity and lower HRQoL, while Piccini and colleagues controlled for 18 covariates including 10 comorbidities and found that, in this context, post-ablation patients with recurrent AF had a similar HRQoL to those who maintained NSR (Piccini et al., 2020). These findings are indicative of the vast diversity in AF cohorts.

2.1.6.ii Impact on healthcare systems

AF represents a substantial economic burden for healthcare systems. In the UK, AF is calculated to cost the NHS between £1,435m– £2,548m in the reference year 2020, or between 0.9%–1.6% of total NHS expenditure, rising to 1.4%–4.3% of expenditure by 2040 (Burdett and Lip, 2022); a further study estimates that the number of people with AF will rise to 2,856,489 by 2040 (Camacho and Lip, 2023). Nearly 60% of these costs are related to hospital admissions, a finding broadly corroborated by other studies (Meyre et al., 2019; Freeman et al., 2015): globally, around 30% of people with AF have one hospitalisation episode each year, and 10% have two or more (Steinberg et al., 2014). As inpatient care accounts for the majority of AF-related healthcare costs (Mantovani et al., 2023), this indicates a need to develop effective outpatient and community-based care strategies.

Healthcare resource is also impacted by AF. People with AF have a higher healthcare resource utilisation than those without (Zeitler 2022; Goren 2013), including substantially increased visits to primary care practitioners (Aliot et al., 2010). In UK primary care, Kassianos and colleagues found that the mean cost of managing an AF patient during the first 12 weeks following diagnosis (excluding anti-coagulation costs) was £941, and £426 per patient-year thereafter. If patients were admitted to hospital for AF-related reasons during the first 12 weeks, costs rose to £2,285 per patient (Kassianos et al., 2014).

2.1.7 Current treatments for AF

The current care pathway for AF in England is set out in Clinical Guideline NG196 (National Institute for Health and Care Excellence, 2021). It begins with the assessment of stroke risk using the CHA_2DS_2-VASc tool (Lip et al., 2010) and bleeding risk using the ORBIT tool (O'Brien et al., 2015). Where indicated and preferred, stroke risk is modified using a direct-acting anticoagulant (DOAC), or a vitamin K antagonist if the DOAC is not tolerated or indicated. Following this, rate control is offered as a first-line strategy with a beta-blocker, a calcium-channel blocker, or digoxin, based on symptoms, heart rate, comorbidities and preference. If rate control is not achieved, a second drug is added from this list.

Rhythm control is considered when arrhythmia persists despite rate control success, or where rate control has not succeeded. It takes one of two forms: drug therapy using an anti-arrhythmic (which may be a "pill in the pocket" strategy for infrequent episodes), or electrical cardioversion (in which a controlled shock is delivered to the heart while the patient is sedated, causing a critical mass of cardiac myocytes to depolarise and re-set the abnormal rhythm). Anti-arrhythmic drugs may be used as a supplement four weeks prior and up to 12 months following electrical cardioversion, to help prevent recurrence.

Various forms of ablation are considered if drug therapy or electrical cardioversion do not restore NSR. Ablation, also known as catheter ablation, uses radiofrequency waves or cryotherapy to isolate the pulmonary veins and other sources of ectopic activity in the heart muscle; where AF is persistent, ablation additionally modifies the substrate of both atria to remove cells generating disruptive high-frequency wavefronts. During an ablation procedure the patient is sedated, with catheters delivered percutaneously via the femoral vein. Procedures may take anywhere between one and six hours, depending on the extent of tissue to be ablated (Ang and Earley, 2016).

Refractory AF is treated with titrated or additive medications and/or multiple procedure cycles (National Institute for Health and Care Excellence, 2021), which show diminishing returns and an increase in treatment-related risk (Hindricks et al., 2020).

2.1.7.i Risk factor management

Risk factor management (RFM) targets those risk factors and comorbidities considered to be modifiable (Elliott et al., 2023; Gallagher et al., 2021; Hendriks et al., 2021; Chung et al., 2020; Lowres et al., 2012). RFM is an increasingly important element of the ABC pathway (Bucci et al., 2023; Romiti et al., 2022) (comprising anticoagulation, better symptom control and comorbidity/risk factor management) that is incorporated in various AF management guidelines (Lip, 2023; Hindricks et al., 2020; Andrade et al., 2020; Brieger et al., 2018; Joung et al., 2018; Naser et al., 2017).

Evidence shows associations between RFM programmes and attenuation of AF outcomes including aspects of symptom severity, HRQoL and recurrence after treatment (Elliott et al., 2023; Middeldorp, Kamsani and Sanders, 2023; O'Keefe et al., 2021; Ariyaratnam et al., 2020; Neefs et al., 2019; Nalliah, Sanders and Kalman, 2018; Voskoboinik et al., 2016; Pathak et al., 2014; Abed et al., 2013). For instance, the RACE 3 trial investigated "routine" versus "aggressive" RFM for patients with early persistent AF and concomitant heart failure (De With et al., 2019). The trial randomised 230 patients with persistent AF and concomitant heart failure to receive usual care or usual care plus statins, blood pressure medications, and a cardiac rehabilitation programme consisting of exercise, diet restrictions and behavioural counselling for three weeks before undergoing electrical cardioversion. At 12-month follow-up, improvements in the quality of life measure Short Form (SF)-36 were larger in the RFM group than in the control; interestingly, some domains of improvement were independent of AF recurrence, suggesting that HRQoL in AF is not simply related to absence of symptoms.

As a result of this and similar studies, strong claims have been made for RFM. Majahan et al. suggest it "could retard and reverse the pathological processes underlying AF and reduce AF burden" (2017, p.990). Hong and Glover point out the benefits of lifestyle change not just for AF patients, but also for patients with comorbidities and for global health systems: "Individualized diet prescription, weight loss management, and behavioral therapy may reduce atrial fibrillation-related complications, such as stroke, and the overall burden of disease" (2018, p.2).

In 2017-18, AF researchers called for a change in the existing guidelines to promote "an integrated care model to incorporate risk factor modification as the fourth pillar of AF care in conjunction with established pillars of rate control, rhythm control, and anticoagulation therapy" (Lau et al., 2017, p.583; Calkins et al., 2018). As a result, RFM and the integrated model of AF care (Gallagher et al., 2017) is now a recommendation in guidelines across the world (Hindricks et al., 2020; Andrade et al., 2020; Brieger et al., 2018; Joung et al., 2018), although it does not feature in the current NICE guideline NG196 (National Institute for Health and Care Excellence, 2021).

2.1.8 Issues with current treatments

2.1.8.i Effectiveness of current treatments

In terms of achieving and maintaining NSR, current treatments appear to have variable success – although heterogeneity of patient characteristics, comorbidities and risk factors across study cohorts makes it difficult to obtain a clear understanding of interventions' effect. In summary: pharmacological rate and rhythm control strategies have "reasonable" success in converting to NSR (Hindricks et al., 2020, p.409), particularly with recent-onset and paroxysmal profiles

(Istratoaie et al., 2021; Brandes et al., 2020; McIntyre et al., 2019; Al-Khatib et al., 2014; Dorian and Angaran, 2014; Ulimoen et al., 2013), but these successes result in varying recurrence profiles.

Electrical cardioversion achieves NSR in 50-90% of patients (Shima et al., 2021; Bonfanti et al., 2019; Scheuermeyer et al., 2019; Pokorney et al., 2017) but 42-65% of successfully cardioverted patients experience AF recurrence within 2-52 weeks (Brandes et al., 2020; Hellman et al., 2017; van Gelder et al., 1999).

Ablation has a reported conversion rate of 50-80% (Verma et al., 2015; Ganesan et al., 2013) and a longer-term resistance to recurrence: Winkle et al. (2023) detected a 2% recurrence rate per year after the second year post-procedure, Gaita et al. (2018) found 52% of an ablation cohort to be AF-free after 10 years, and the CABANA trial found 62.5% of a post-ablation cohort free from recurrence at 48.5 months (Russo et al., 2021).

2.1.8.ii HRQoL associated with current treatments

Over the last two decades, investigations of treatments for AF have often included a (health-related) quality of life metric in addition to disease-specific or comorbidity-related outcomes. The broad conclusion is an inverse correlation between HRQoL and AF symptom severity.

In summary: corresponding with their smallest magnitude of symptom control compared with other AF treatments, pharmacological rate and rhythm control are associated with the smallest magnitudes of HRQoL improvement (Miura et al., 2020; Mark et al., 2019; Ha et al., 2014). Electrical cardioversion has a higher conversion rate but a lower maintenance rate, and is associated with some improvement in HRQoL (Morken et al., 2022; Ha et al., 2020; Sandhu et al., 2017). Ablation appears to have the highest success rate in achieving/maintaining NSR, and also has the highest associated HRQoL of conventional treatments (Gupta et al., 2021b; Buist et al., 2020; Jain et al., 2020; Blomström-Lundqvist et al., 2019; Pezawas et al., 2016; Andrade et al., 2014).

This seemingly simple association between HRQoL and symptom attenuation should not be taken at face value: absence of symptoms does not automatically confer improved HRQoL. Dorian and Angaran (2017) discuss the apparent paradox whereby patients' self-reported HRQoL improves by similar magnitudes after either ablation or antiarrhythmic drugs, despite the fact that ablation yields greater, and longer-lasting, symptom improvement than antiarrhythmics. Similarly, some studies note a persistent improvement in HRQoL despite post-treatment recurrence (Mohanty and Natale, 2021; Ha et al., 2020; Piccini et al., 2020; Sandhu et al., 2017); this is attributed to the positive effect of treatment expectation, but hardly provides sufficient explanation for consistent HRQoL in the context of failed treatment (El-Haddad, Hegazi and Hu, 2020).

It is also noticeable that while many quantitative studies detect improved post-treatment HRQoL scores, qualitative studies consistently identify post-treatment problems – including psychological, social and treatment-related concerns – that explicitly detract from patients' own concepts of HRQoL (Holmlund et al., 2022; Wang et al., 2022; Jones et al., 2020; McCabe et al., 2020; Bergtun, Oterhals and Fridlund, 2019; Stridsman et al., 2019; Taylor et al., 2018; Thrysoee et al., 2018; Rush et al., 2017; Doyle, Lloyd and Davis, 2011). There appears to be a discrepancy between HRQoL improvement, as detected by quantitative scales, and HRQoL deterioration, as detected by qualitative enquiries; this may be an effect of publication bias, or perhaps insensitivity in quantitative HRQoL scales to the nuances of the lived experience of quality of life. Mixed methods approaches may be important in future trials of AF treatments, to allow an inter-related analysis of quantitatively- and qualitatively-reported HRQoL outcomes in this complex condition.

2.1.8.iii Safety of current treatments

While many people with AF experience a balance of benefits and disadvantages from treatment, side-effects and adverse responses are common and well-documented.

The side-effects of rate- and rhythm-control medications include nausea and vomiting, dizziness, headache, gastro-intestinal disturbance, oedema, hypotension, bradycardia and xerostomia; several-side effects are those associated with AF itself, including arrhythmia, palpitations, dyspnoea, fatigue and cardiac conduction system disorders (British National Formulary, 2023a, 2023b, 2023e, 2023f, 2023c, 2023d, 2023j; Abraham et al., 2022; Gupta et al., 2021a).

Some medications, particularly those used to maintain sinus rhythm after cardioversion, have a pro-arrhythmic propensity and may also contribute to heart failure, hypo- and hyperthyroidism and cardiac conduction system disorders such as atrioventricular block (British National Formulary, 2023g, 2023h, 2023i; Taylor, Hodgkinson and Hobbs, 2010; Doyle and Ho, 2009).

Biancatelli et al. (2019) found that the anti-arrhythmic amiodarone may provoke greater arrhythmia, ocular adverse effects, pulmonary toxicity and acute respiratory distress syndrome. Pokorney et al. (2020) found higher all-cause mortality in ORBIT-AF patients prescribed amiodarone (HR 2.06 (95%CI=1.35–3.16)) than patients taking other antiarrhythmics. Where clear conclusions on safety cannot be drawn, clinicians trade HRQoL against effectiveness in making prescribing decisions. Thus Reimold and Reynolds (2018, pp.2–3) suggest that "safety may come first, but it is not everything… the price that is paid in terms of nuisance adverse effects, as well as potentially serious toxicity with long-term use, at least comes with clear evidence that [amiodarone] is more effective than other drugs."

Electrical cardioversion is associated with lower incidence of serious adverse events, but is not entirely risk-free. Stiell et al. found that older age, coronary artery disease and use of fentanyl were

associated with higher risk of adverse events (Stiell et al., 2021), while Pokorney and colleagues (2017) found that cardioversion did not prevent AF progression, and was associated with an increased risk of cardiovascular hospitalisation in the 12 months after cardioversion (adjusted HR 2.2 (95%CI=1.8-2.8)). Other studies found positive associations between electrical cardioversion and brady-arrhythmias in older patients and acute ischaemic stroke, particularly in emergency cardioversions (Rasmussen et al., 2022; Huang et al., 2022; Forslund et al., 2021). Against this, Bonfanti et al.'s study of 419 emergency cardioversions found no serious adverse events (Bonfanti et al., 2019), while Son et al., in a cohort of 1,718 elective patients, found only 0.47% with either minor stroke, TIA or sinus node dysfunction (Son et al., 2020).

The safety of ablation appears to be good in comparison to antiarrhythmic drugs, with a lower risk of thromboembolic or cardiovascular events, including hospitalisations (Saad-Omer et al., 2020; Mansour et al., 2018). Periprocedural complications seem also to be low (Russo et al., 2021; Wynn et al., 2016); a recent individual patient meta-analysis found an overall periprocedural complications rate of 4.51% (95%CI=3.8–5.3%), which appears to be decreasing over time (Benali et al., 2023). There is variability in safety-related outcomes depending on the procedural methods used, patient characteristics, AF type, type/duration of periprocedural medication use, and the ablation centre's volume of annual procedures (Charitakis et al., 2022; Müller et al., 2022; Watanabe et al., 2022; Natale et al., 2021; Freeman et al., 2018; König et al., 2018); in particular, female sex appears to be a risk factor for adverse events, AF recurrence and a higher risk of hospitalisation post-ablation (Mszar et al., 2023; Li et al., 2020b).

Despite a currently under-researched evidence-base on harms, it is clear that RFM is also not without its safety issues. In particular, pharmacotherapy of underlying conditions may confer an even greater level of polypharmacy than guideline-directed primary treatments for AF (Chen et al., 2020), with increased attendant risks. Additionally, RFM trials are designed on a spectrum of "aggression": intensively-managed programmes of combined pharmacotherapy, diet, exercise and educational classes delivered by clinicians, which may not promote the self-efficacy – the individual's belief in their own capacity to effect desired change (Peters et al., 2019; Bandura, 1977) – necessary to promote adherence and behavioural change in the longer-term (Okuboyejo, Mbarika and Omoregbe, 2018; Náfrádi, Nakamoto and Schulz, 2017; Martos-Méndez, 2015). The approach is typified by the Aggressive Risk Factor Reduction Study (ARREST-AF) prior to ablation (Gallagher et al., 2016; Pathak et al., 2014). Following up its participants over a mean of 41.8 months, ARREST-AF found excellent outcomes in the RFM group (0 participants with HbA1c ≥7%, systolic blood pressure 126.8±12.8, BMI 29.1±3.9, self-reported AF episode severity of 3.3/10±1.5). Longer-term follow-ups of adherence in addition to outcomes – which could usefully include HRQoL – should be scheduled in aggressive RFM trials, together with qualitative investigations of

participant beliefs and feelings regarding RFM, to identify the extent of adherence and any associated barriers or enablers.

In summary, conventional treatments for AF are associated with undesirable side-effects and risks, which may offset benefit gained.

2.1.8.iv Polypharmacy and AF

A diagnosis of AF may contribute to what Duerden et al. term "problematic" polypharmacy, in which patients take multiple medications that cause their own health-related problems independent of the conditions for which they are prescribed (Duerden et al., 2013). Polypharmacy has become a prevalent issue for several reasons including the single-disease focus of clinical guidelines, and the increase in population longevity which is associated with increased multimorbidity (Specialist Pharmacy Service, 2022; Delara et al., 2022; Guo et al., 2022b). For healthcare services, polypharmacy represents the increased costs of more frequent patient monitoring and healthcare resource utilisation to deal with downstream consequences such as hospitalisations and increased GP visits (Specialist Pharmacy Service, 2022). This is additional to the cost of medications themselves: polypharmacy is thought to play a significant role in the NHS's 5% annual increase in spending on medicines, an increase that is growing "substantially faster than the total NHS budget" (Ewbank et al., 2018, p.2).

For people with AF, the NICE care pathway lends itself to a potentially high polypharmacy baseline, to which is added the possibility of additional pharmacotherapy for comorbidities such as hypertension, dyslipidaemia, diabetes, heart failure and COPD. An individual patient meta-analysis of 33,602 people with AF found that 42.7% had moderate polypharmacy (5-9 medicines) while 20.7% had severe polypharmacy (>9 medicines) (Gallagher et al., 2020); another study found that of 2,712 Balkan AF patients, 2,263 had ≥2 additional comorbidities and 55.5% had polypharmacy (Kozieł et al., 2021).

Problematic polypharmacy is linked with risks to individual patients including impaired HRQoL and increased risk of mortality, adverse drug reactions and hospitalisation (Delara et al., 2022; Shaikh et al., 2018; Dagli and Sharma, 2014). One study found that polypharmacy in AF patients carried a HR for cardiovascular death of 1.5 (95%CI=1.2–1.8) (Proietti et al., 2016b), while another identified a HR of 1.3 (95%CI=1.1–1.6) for all-cause mortality in patients taking ≥9 medications (Millenaar et al., 2021). Chen et al. (2020) found an increased risk of major bleeding (HR 1.2, 95%CI=1.1–1.2) and heart failure (HR 1.3, 95%CI=1.3–1.4) in patients ≥75 years with ≥5 active prescriptions at the point of AF diagnosis, while Millenaar et al. (2021) followed patients of mean age 71.5 years for two years and found an increased risk of adverse outcomes in those with ≥9 medications, including all-

cause mortality (HR 1.3, 95%CI=1.1–1.6); Martínez-Montesinos et al. (2023) put the HR of a composite thromboembolitic endpoint as high as 1.6 (95%CI=1.1–2.3) for ≥5 medications.

The emergence of risk factor management (RFM) and the ABC approach to treatment may pose additional polypharmacy risks for people with AF; no polypharmacy or specific harms analysis has yet been published regarding RFM, although long-term follow-ups to trials such as the RACE series (De With et al., 2019) may include this.

2.1.8.v Patients' experience of treatment

Patients' experience of treatment, as described in qualitative studies, indicates a balance of positive and negative experiences. Symptomatic relief is described as highly positive, enabling a return to normal activities, socialising and working (Rush et al., 2017; Lane et al., 2015).

However, patients' accounts of medication regimes often suggest negative side-effects that detract from the levels of AF symptom relief gained. Patient-focused websites describe patients' side-effects on medication including headaches, cold feet, tinnitus, dyspnoea, fatigue, low mood, xerostomia, aversion to exercise and skin sensitivity to sunlight (AF Association, 2022; Healthtalk, 2019a). Medications are, in general, a source of anxiety, fear and stress (Stridsman et al., 2019; Salmasi et al., 2019b).

Patients' experience of procedures for AF is more mixed; while there is improvement in mood, self-image and HRQoL with positive outcomes from electrical cardioversion and ablation, there are also themes of anxiety about possible recurrence, disappointment about actual recurrence, fear about the procedures themselves and reluctance over pre- and post-procedure medications (Wang et al., 2022; Bergtun, Oterhals and Fridlund, 2019; Healthtalk, 2019b; Mccabe, Rhudy and Devon, 2015).

The wider treatment environment and the process of securing treatment, including interaction with healthcare professionals and the diagnostic process, reveals a level of dissatisfaction that may impact on HRQoL (Holmlund et al., 2022; Noseworthy et al., 2019; Bakhai et al., 2013). A "fragmented" care system, with limited communication between primary, acute and specialist services, is experienced as a source of stress that may worsen symptoms (Bergtun, Oterhals and Fridlund, 2019; Lane et al., 2015); it is also a source of risk for polypharmacy (Duerden et al., 2013). People with AF often wish to support themselves and be proactive in managing their symptoms (Redman et al., 2017), but may exit a diagnosis uncertain about the nature of AF (Healthtalk, 2019c; Thrysoee et al., 2018), feeling dissatisfied by the lack of information given by healthcare professionals about self-management and/or self-care (Wilson and Rush, 2021; McCabe et al., 2020; Salmasi et al., 2019a; Taylor et al., 2018; Redman et al., 2017; Borg Xuereb, Shaw and Lane, 2016; Mccabe, Rhudy and Devon, 2015; Bakhai et al., 2013).

2.2 Complementary therapies for AF

A definition of the term "complementary therapies" is given in **3.2.1.i below**.

When used adjunctively with usual care for AF, complementary therapies may offer a useful enhancement to the range of therapeutic options for several reasons:

- Complementary therapies operate on a holistic model, "treating the patient, not the disease" (Birch, 2019a). This offers advantages over the disease-specific treatment model of conventional medicine (Payne, 2016) for complex conditions such as AF, in which a range of risk factors and comorbidities may be considered as much a therapeutic target as the AF itself – a strategy that may impact on equally on HRQoL and symptoms (Mbizo et al., 2018; Alwhaibi, Bhattacharya and Sambamoorthi, 2015). This tallies well with the "look beyond the ECG, treat the patient" approach (De With et al., 2019; Alings et al., 2013) that has emerged in AF therapeutics. In addition, the typical combination of specific and non-specific effects in complementary therapies may benefit overall wellbeing in AF patients and improve symptoms and outcomes for a range of comorbid conditions in addition to those associated with AF (Sharp et al., 2018);
- Overall, the safety record of complementary medicine is good, particularly in the hands of appropriately qualified professionals – although it must be noted that a good safety record may be partly a function of under-reporting due to the widely unregulated status of complementary medicine. However, in general, research shows that complementary therapies are associated with lower levels of risk than conventional treatments for AF, and fewer, less serious side-effects (Bäumler et al., 2021; Li et al., 2020a; Pratt et al., 2020). Complementary therapies also avoid adding to the polypharmacy burden of conventional drugs, and may attenuate the side-effects of other medications (Sommers, Vinjamury and Noborikawa, 2021; Chen et al., 2018b). They have also been shown to reduce healthcare resource usage for some conditions including the physical and emotional effects of cancer (Tillery and McGrady, 2018), medication usage including antibiotics (Baars et al., 2019) and opioids (Hassan et al., 2020).
- Use of complementary therapies may benefit patients by promoting self-efficacy (Wenham et al., 2018) and increased self-care through support for lifestyle change (Pinto et al., 2022; Bishop et al., 2019), which may additionally impact on comorbidities in addition to AF. This may support change for the four modifiable lifestyle factors of physical inactivity, alcohol consumption, smoking and obesity (Foy et al., 2018) that represent strong risks for incident AF. Modifying lifestyle factors may contribute to clinician-guided medication reduction and decreased healthcare resource usage, which may additionally benefit

national health delivery systems relating to typically multimorbid conditions such as AF (Jacobs and Fisher, 2013);

- Some complementary therapies demonstrate strong evidence of longitudinal effects (Vickers et al., 2018; Lewith, 2012; Thomas et al., 2006). Such effects may support longer-term cost-utility to offset against short-term costs of therapy delivery.

In general, complementary therapies are under-researched and lack rigorous investigation of effect, which leads to a poor-quality and inconsistent evidence-base (Lewith, 2012; Black and Rowling, 2009). Despite this, many patients choose to use complementary medicine either adjunctively to conventional medicine, or as an alternative (Sharp et al., 2018; Yang, Adams and Sibbritt, 2017; Lorenc et al., 2012; Hunt et al., 2010; Bishop, Yardley and Lewith, 2006; Yeh, Davis and Phillips, 2006; Cohen, Ek and Pan, 2002; Goldbeck-Wood et al., 1996). Specifically for AF, in a study of online discussions, Redman et al. (2017) noted that AF patients actively sought complementary therapies and discussed them in peer forums; it has been suggested that some patients use complementary therapies for arrhythmias without the knowledge of their conventional healthcare practitioner (Brenyo and Aktas, 2014). In a 2012 literature review, Grant and colleagues found that complementary medicine usage amongst patients with cardiovascular disease was widespread (up to 64.0% of patients), and thought by a small proportion of users to be of greater benefit than conventional medications; 59.0% of patients had sought complementary medicine due in part to adverse responses to conventional medicine (Grant et al., 2012); Wood et al. (2003) noted that 58.0% of 107 survey respondents were taking nutritional supplements in addition to a cardiovascular medication such as digoxin, warfarin, sotalol or amiodarone. In the eyes of Ng et al. (2022b), this usage in itself gives a rationale for conducting research into complementary medicine:

> "The very fact that patients actively choose to use [complementary] therapies, with many lacking safety and efficacy profiles, justifies the conducting of research in this field. New knowledge gained in turn, can be incorporated into the medical curriculum, and can help inform shared decision-making between healthcare practitioners and patients." (p2)

2.3 Studying appropriate outcomes

Recent publications have noted the variation in outcomes, measurement instruments and follow-up durations (Qiu et al., 2019) in investigational studies of AF. A recent consensus study by the AF working group of the International Consortium for Health Outcomes Measurement (ICHOM) brought together AF experts and patients to define an international standard set of outcome measures for use in AF research (Seligman et al., 2020). The set was defined under three domains:

long-term consequences of disease; complications of treatment; and patient-reported outcomes. The patient-reported outcomes domain was divided into seven sub-domains, derived from the most important concerns of the working group's patients: health-related quality of life (HRQoL), emotional functioning, physical functioning, exercise tolerance, symptom severity, ability to work, and cognitive functioning.

To align with the principles of the ICHOM value-based outcomes framework, and to enable comparisons of new therapeutic options with existing equivalents, a future large-scale trial should aim to test the patient-reported outcome sub-domains of HRQoL and symptom severity, while also considering the domain of treatment complications (i.e., reporting on intervention harms).

In alignment with guidance on investigating complex interventions, which may effect change across a range of domains (Skivington et al., 2021b), a future large-scale trial may also choose to investigate a wider spectrum of outcomes including healthcare resource usage, the effect of interventions on comorbidities, and adherence to self-care/lifestyle advice. This feasibility study collected data on all the above outcomes, to test the feasibility of data collection.

2.4 Rationale for a systematic review

As demonstrated above, current conventional treatments for AF offer limited symptomatic relief and have varying associations with HRQoL; all are associated with levels of risk. Complementary medicine may present a helpful adjunct to current treatment options, and may attenuate AF symptoms, attenuate comorbidities and/or their symptoms, support patients with self-care, and improve HRQoL over time, with lower levels of risk and fewer undesired side-effects than conventional treatments.

The last decade has seen an increase in research into complementary therapies for AF. Various reviews have attempted to synthesise the current evidence, focusing on either a single therapy such as Chinese herbs (Lei et al., 2021) or a number of therapies such as Chinese herbs, yoga and acupuncture (Abdul-Aziz et al., 2018; Kanmanthareddy et al., 2015; Brenyo and Aktas, 2014). The following systematic review investigates whether there is evidence for the effect of complementary therapies for symptoms and HRQoL in AF.

An additional rationale for conducting a systematic review is to discover the current state of evidence in the topic area, including the question of whether a comparable trial has already been conducted (O'Leary et al., 2017; Maggio, Sewell and Artino, 2016). A literature review evaluating the current evidence for the effect of the interventions in a future trial therefore represents a preliminary aspect of feasibility for the future trial, and is an important contributor to the avoidance

of research waste (Khalil et al., 2022; Blaine, Brunnhuber and Lund, 2021; Glasziou and Chalmers, 2018).

3 Systematic review

This chapter synthesises the current evidence for the effect of complementary therapies in attenuating symptoms and improving HRQoL in atrial fibrillation. Ten studies were included, representing four complementary therapies; all were of poor reporting quality, high or "some concerns" risk of bias, and a high degree of clinical and methodological heterogeneity that rendered statistical synthesis inadvisable. The chapter concludes by drawing together the rationale for a future trial and this feasibility study, and setting out the feasibility study's research question, aim and objectives.

This review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 reporting guideline (Page et al., 2021b) and the Synthesis Without Meta-analysis (SWiM) guideline (Campbell et al., 2020). The protocol was registered on the PROSPERO register of systematic reviews on 30/3/21 (registration number CRD42021244730).

3.1.1 Systematic review abstract

Atrial fibrillation (AF) is the most common arrhythmia globally, associated with an increased risk of stroke, debilitating symptoms and an overall decrease in health-related quality of life (HRQoL). Current treatments for AF may not always provide symptomatic relief or increase HRQoL. This systematic review examined evidence for the effect of complementary therapies on symptoms and HRQoL in people with AF.

Searches were conducted in 66 sources in March 2023 and updated in October 2023. Trials were included if they investigated one or more of 18 complementary therapies for current AF and reported outcomes including at least one measure of symptoms or HRQoL.

Eight randomised controlled trials and two non-randomised studies were included, with an effective total of 1,128 participants at baseline. Four therapies were investigated: yoga (n=4), Chinese herbal medicine (n=3), acupuncture/acupressure (n=2) and a dietary supplement (n=1). All studies were assessed either at high or "some concerns" risk of bias, using Cochrane's Risk of Bias 2.0 (RoB2) tool; this was exacerbated by poor reporting, confirmed by a CONSORT analysis. A high degree of clinical heterogeneity was observed in the included studies; this, plus the small number of studies included for each therapy, made it inadvisable to undertake statistical synthesis and infeasible to grade the certainty of evidence for each outcome.

Outcome statistics were presented for each outcome domain together with visual representations of directions of effect (harvest plots). In the symptoms domain, 18 of a total 21 outcome measures from all 10 studies favoured the intervention (92.3% observations), while two showed no effect (4.9% observations) and one favoured the control (2.7% observations). In the HRQoL domain, 25

of a total 28 outcome measures from four studies favoured the intervention (88.3% observations), while one showed no effect (3.7% observations) and two favoured the control (7.9% observations). A descriptive synthesis was carried out to investigate the safety of the included studies, which was comparable with other studies of safety in complementary therapies.

Recommendations for future research align with the findings of other reviews of complementary therapies, including a recommendation that review teams should search a wide range of sources to identify relevant studies that may not be published in readily accessible sources. This review also recommends backward citation searching on analogous reviews, and the inclusion of at least one team member able to retrieve and translate records and studies from non-English language bibliographic sources. Future researchers should collect data on a range of effect modifiers, outlined in this review, and control for these when investigating the effects of interventions for AF in primary or secondary research. Finally, this review has limited generalisability to real-world contexts because all included studies used a standardised protocol or an isolated element of the therapy in question, which is not representative of real-world practice; future investigational studies are recommended, using a more pragmatic version of the investigated therapies to give greater generalisability to real-world contexts.

3.1.2 Objectives of this review

The objectives of this review were:

1. To assess the evidence for the effectiveness of individual complementary therapies for symptoms and HRQoL in AF;
2. To synthesise safety in the included studies (Cumpston and Chandler, 2022).

3.1.3 Research question for this review

The research question for this review is: What is the evidence for the safety and effect of complementary therapies on symptoms and HRQoL in people with atrial fibrillation?

3.1.4 Deviations from the review protocol

The protocol for this review specified that only reports of parallel-group RCTs would be included; however, the final review included two studies that were not randomised and did not use a parallel-group design (Lakkireddy et al., 2013 and Lombardi et al., 2012). In addition, the protocol specified that only peer-reviewed full reports would be included, but one study (Kodliwadmath et al., 2021) was included although it was only available as a conference abstract. These departures from the protocol are justified below (**3.3.5** and **3.6.1.ii**).

The protocol also defined the "symptoms" domain as only frequency of AF episode or presence/absence of AF. On reviewing the relevant literature, this criterion excluded the majority of identified papers, and a decision was therefore taken to expand this criterion to allow the inclusion of any symptom measure as defined by the current ESC guideline (Hindricks et al., 2020).

Finally, no analysis was carried out on the age characteristic between groups (to determine heterogeneity as a proxy for judging integrity of randomisation) as stipulated in the protocol, due to the sample size of most trials being too small to reliably indicate heterogeneity that could not be ascribed to chance.

3.2 Definition of terms

3.2.1 Complementary medicine and complementary therapies

The conceptual basis of complementary medicine (CM) is fluid and leads to a difficulty in definition. Current definitions predicate CM on its exclusion from biomedicine or the "mainstream medical model" (Wieland, Manheimer and Berman, 2011); for instance, the World Health Organization proposes that CM is "a broad set of health care practices that are... not fully integrated into the dominant healthcare system" (World Health Organization [WHO], 2019, p.8), and the US National Library of Medicine's descriptor data for the Medical Subject Heading (MeSH) term *Complementary Therapies* defines CM as "therapeutic practices which are not currently considered an integral part of conventional allopathic medical practice" (National Library of Medicine, 2023, p.1). The terms *complementary*, *alternative* and *integrative,* often used interchangeably, denote differences of use rather than any substantive quality of the therapy itself (National Library of Medicine, 2020a; National Center for Complementary and Integrative Health, 2018). And while many complementary therapies are defined as such on the grounds of paradigmatic dissonance with biomedicine, some (Western herbalism, nutritional therapy and others) are firmly rooted in biomedical paradigms and deemed complementary by sole virtue of their exclusion from the purview of (most) national state healthcare delivery systems (Bush et al., 2020; Koithan and Devika, 2010). This exclusionary definition is itself complicated by the approach of *integrative* medicine, which seeks to include complementary approaches alongside those of conventional medicine in a package of care (National Center for Complementary and Integrative Health, 2018).

These difficulties have led researchers to supplement conceptual or theoretical definitions with a seemingly simple expedient: the "operational definition", otherwise known as a comprehensive list of all therapies that could be considered complementary. The first work in this area was published in

2011 by the Cochrane Complementary Medicine (CCM) group (Wieland, Manheimer and Berman, 2011; Cochrane Complementary Medicine, 2017a, 2017b), and was updated and expanded in 2022 (Ng et al., 2022b, 2022a). The work of the CCM group has not resolved the epistemological issues, but it has at least offered an authoritative basis for practice in researching complementary medicine.

3.2.1.i Defining complementary therapies

As the feasibility study and any future trial were to be carried out in the UK, the list of investigated therapies was limited to those practised in the UK, and more specifically to those listed by two UK Government-supported healthcare bodies representing a UK-wide availability:

- Individualised therapies listed by the UK NHS Health A-Z website at 27th February 2023 (National Health Service, 2023). These were: Acupuncture; Alexander Technique; Chiropractic; Herbal medicines; Homeopathy; Hypnotherapy; Osteopathy.
- Additional individualised therapies voluntarily registered as Profession Specific Boards (PSBs) with the Complementary and Natural Healthcare Council (CNHC) at 27th February 2023 (Complementary and Natural Healthcare Council (CNHC), 2023). These were: Aromatherapy; Bowen Therapy; Craniosacral Therapy; Kinesiology; Massage Therapy; Naturopathy; Nutritional Therapy; Reflexology; Reiki; Shiatsu; Yoga Therapy.

Some therapies listed on the CNHC website were excluded as they fall outside the CCM group's definition of complementary medicine (Ng et al., 2022b): these were colon hydrotherapy, sports therapy and all exercise therapies except mind-body exercise such as Tai Chi, yoga or Qi Gong.

Brief definitions of each included therapy can be found in **Appendix E**, item 1.

3.2.2 Quality of life

In discussing the concept of "quality of life", this review and feasibility study accept the definitions proposed by Guyatt et al. (2007) in defining quality of life (QoL) as "a broad concept that relates to all aspects of human life… [whereas] [health-related quality of life] HRQoL denotes a focus on the effects of illness and treatment on quality of life" (pp.1229-30). In the literature, the two terms are often used interchangeably (Karimi and Brazier, 2016; Lin, Lin and Fan, 2013); this review uses the term "health-related quality of life" (HRQoL) as the relevant term throughout, unless specifically noted otherwise.

3.2.3 Symptoms

Symptoms were defined as a list taken from the European Society of Cardiology guidelines for diagnosis and management of atrial fibrillation (Hindricks et al., 2020). These were: palpitations/tachycardia, dizziness, fatigue, breathlessness, chest pain, syncope, exercise intolerance, disordered sleep and depression.

3.3 Search and selection process

3.3.1 Search strings

The Cochrane Complementary Medicine (CCM) group's operational definition was the most up-to-date search string available to this review (Ng et al., 2022b, 2022a), and was also more comprehensive than the PubMed Complementary Medicine filter (National Library of Medicine, 2019) or the Cochrane Complementary Medicine search string for CENTRAL (Cochrane Complementary Medicine, 2017a). The Cochrane operational definition was therefore adapted for this review to include only synonyms for the therapies included in the UK-centric list set out above.

Table 1 (overleaf) shows an outline of the generic search strategy as adapted to this review's therapies, with appropriate MeSH terms. Only the P and I elements of PICO (Richardson et al., 1995) were included in the initial searches, to balance sensitivity and specificity (Bramer et al., 2018). Full strings, and their adaptations for each source searched, are available via **Appendix E**, item 2 and item 5.

Table 1: Outline of generic search strategy

	Population	Intervention
Primary search term	Atrial fibrillation	Complementary therapies
MeSH term	Atrial Fibrillation	Complementary Therapies (exploded)
Free-text synonyms *(main terms only)*	Atrial fibrillation, Auricular fibrillation, Heart atrium fibrillation, Heart atria fibrillation, Cardiac atrium fibrillation, Cardiac atria fibrillation	**General:** Alternative Medicine/Therapy, Complementary Medicine/Therapy, Integrated Medicine/Therapy **Acupuncture:** Acupressure, Acupuncture, Acupuncture therapy, Auricular Acupuncture, Electroacupuncture **Alexander Technique:** Alexander Method, Alexander Proprioception, Alexander Technique **Aromatherapy:** Aromatherapy, Essential Oils **Bowen Therapy:** Bowen Therapy, Bowen Technique **Chiropractic:** Chiropractic, Chirotherapy, McTimoney, Spinal Manipulation **Cranio-sacral therapy:** Cranial Osteopathy, Cranio-sacral Therapy **Herbal medicine:** Herbal Medicine, Kampo, Phytotherapy **Homeopathy:** Homeopathy, Homotoxicology **Hypnotherapy:** Autogenic Training, Hypnotherapy **Kinesiology:** Kinesiology **Massage therapy:** Bodywork, Manipulative therapy, Manual Lymphatic Drainage, Massage, Myofascial Release **Naturopathy:** Natural Medicine, Nature therapy, Naturopathy **Nutritional therapy:** Diet therapy, Food, Nutrition, Nutritional therapy, Personalised nutrition/diet, Individualised nutrition/diet, Nutrigenomics, Functional medicine **Osteopathy:** Joint Manipulation, Musculoskeletal Manipulation, Osteopathy **Reflexology:** Foot Therapy, Reflex Locomotion, Reflexology, Reflexotherapy **Reiki:** Energy Medicine, Energy therapy, Healing Touch, Reiki **Shiatsu:** Shiatsu **Yoga therapy:** Yoga, Yoga therapy

The generic search string was checked by the reviewer for technical accuracy and relevance to the research question using the PRESS Evidence-Based Checklist (McGowan et al., 2016). UK spelling variants were added. The string was then tested on the Cochrane CENTRAL, MEDLINE and Embase databases to check it was retrieving a range of known literature. These papers were read to extract additional free-text synonyms, which were added to the generic search string.

3.3.2 Sources searched

A proportion of complementary therapy literature is published in languages other than English (LOEs), and may not be readily available via commercial academic publishing channels (Wider and Boddy, 2009; Pilkington et al., 2005). To identify literature relating to the relevant complementary therapies, avoid bias in the review, and maintain validity and generalisability of the results (Guo et al., 2022a; Vassar et al., 2017; Xue et al., 2016; Cohen et al., 2015; Purgato, Cipriani and Barbui, 2012), this review searched a wide range of sources including international databases, national and regional websites and therapy-specific resources. Additionally, a range of grey literature

repositories, including databases of theses and conference proceedings, supplemented the main bibliographic resources (Ahmed, Sutton and Riley, 2012).

The Cochrane Handbook for Systematic Reviews of Interventions (CHSRI) identified eight bibliographic databases identified for searching (Lefebvre et al., 2022a); see **Table 1**. To supplement this, a search of MEDLINE was carried out in August 2020 using the MeSH string *exp Complementary Therapies AND (Databases as topic OR Databases, bibliographic)* to identify further repositories with possible complementary therapies content. Results were filtered to show publications from the previous 10 years, on the grounds that earlier publications were less likely to cite currently operational databases. The search returned 114 results which were screened for relevance using title and abstract; 32 records were excluded. Eighty-two full-text articles were read and a further 64 were excluded. The main reasons for exclusion were: database(s) already identified (40); not relevant to complementary therapies (12); or not citing at least one database with complementary therapies content (12). The remaining 18 articles yielded details of 69 complementary therapies databases. In addition, contact searching (using the researcher's network of professional contacts) identified two further articles (Choi et al., 2014; Cogo et al., 2011). These two papers identified a further 18 databases (total of 87 databases).

To mitigate the self-referential nature of a database search for databases, and to maximise the possibility of finding trials of complementary medicine, a general internet search was carried out in March 2023 using Google (Google/Alphabet Inc., 2023), entering the primary search terms in **Table 1** with the word "research". Thirteen repositories were identified. Results returned by internet search engines are neither as transparent nor reproducible as searches carried out in bibliographic databases, due to dynamic changes in algorithms that search internet content (Haddaway et al., 2015); Lefebvre and colleagues also note the move towards personalisation on the part of internet search engines, which may return different results for identical searches based on the location and identity of the person searching (Lefebvre et al., 2022a). Nonetheless, this search identified some important sources that would otherwise have been omitted.

In March 2023, all 100 identified repositories were investigated for:

1. **Operational** status;
2. **Accessibility**, i.e., free to search and accessible to a UK-based researcher. Where interfaces were in languages other than English, Cloud Translate was used to translate the interface (Google, Inc., 2023). If translations did not render the interface sufficiently clear to search with confidence, the source was excluded;
3. **Relevance**, i.e., containing details of trials and/or systematic reviews of complementary therapies in this review).

Thirty-four repositories were excluded. For a full list of all sources investigated, and the reasons for any exclusion, see **Appendix E**, item 3. **Table 2** shows the full list of bibliographic sources included in the search.

Table 2: Bibliographic sources searched

Search #	Source (location/scope)
1	**CENTRAL** (Cochrane Central Register of Controlled Trials) (UK/international)
2	**MEDLINE** (Ovid) (International)
3	**Embase** (Ovid) (International)
4	**AMED** (Allied and Complementary Medicine) (Ovid) (UK/International)
5	**Cumulative Index to Nursing and Allied Health Literature (CINAHL) Ultimate** (EBSCO) (International)
6	**Cochrane Database of Systematic Reviews (CDSR)** (International)
7	**Epistemonikos** (International)
8	**AltHealthWatch** (US/International)
9	**RISS4U** (Korea)
10	**DBPia** (Korea)
11	**KMBase** (Korea)
12	**OASIS** (Korea)
13	**China National Knowledge Infrastructure (CNKI):** Chinese Hospital Knowledge Database (CHKD) (China)
14	**Wanfang Med Online** (China)
15	**Ostemed** (USA/International)
16	**HOMIS** (Switzerland)
17	**CORE-Hom** (Germany)
18	**Livivo** (Germany)
19	**Japan Science and Technology Information Aggregator (J-STAGE)** (Japan)
20	**AcuTrials®** (US/International)
21	**ABIM** (A Bibliography of Indian Medicine) (Netherlands/India)
22	**National Online Periodicals Repository (NOPR)** (India)
23	**AYUSH Research Portal** (India)
24	**HerbMedPro** (US/International)
25	**Electroacupuncture Knowledge** (UK/International)
26	**Virtual Health Library** (Caribbean/South America)
27	**WHO Institutional Repository for Information Sharing** (IRIS) (International)
28	**WHO PAHO Institutional Repository for Information Sharing (PAHO IRIS)** (International)
29	**WHO Global Index Medicus** (International)
30	**Scientific Electronic Library Online** (SciELO) (International)
31	**Caribbean Public Health Agency** (CARPHA) Evidence Portal (Caribbean)
32	**Qigong and Energy Medicine database™** (UK/International)
33	**SMS Literature database** (Germany/International)
34	**CAMBase** (Germany/International)
35	**Index to Chiropractic Literature** (USA/International)
36	**KoreaScience** (Korea)
37	**Korea Citation Index** (KCI) (Korea)
38	**KoreaMed** (Korea)

Table continued overleaf

Search #	Source (location/scope)
39	**Korean Traditional Knowledge Portal** (KTKP) (Korea)
40	**Acudoc2** (France)
41	**Répertoire des données probantes en acupuncture** (Directory of Evidence in Acupuncture) (France)
42	**Nutrition Evidence** (UK/International)
43	**INAHTA** (Europe/International)
44	**AHRQ EPC Reports** (USA)
45	**NCCIH Selected Research Results** (USA)
46	**National Institute for Complementary Medicine, Health Research Institute** (Australia)
47	**National Research Centre for Complementary and Alternative Medicine** (NAFKAM) (Norway)

3.3.2.i Grey literature

Grey literature, defined as that produced by "government, academics, business and industry in print and electronic formats, but… not controlled by commercial publishers" (Farace and Frantzen, 2004), may play an important role in systematic reviews by mitigating publication bias that may inflate treatment effect (Ayorinde et al., 2020; Paez, 2017; Hopewell et al., 2007). In addition, the inclusion of grey literature provides a more comprehensive view of the available evidence (Paez, 2017; Winters and Weir, 2017; Mahood, Van Eerd and Irvin, 2014). However, a grey literature search may not yield many eligible results: in a sample of 129 reviews, Hartling et al. (2017) found that grey literature typically represented only 2% of studies included in the final review. Nonetheless, sources of grey literature should be searched in a systematic way (Godin et al., 2015), as studies of complementary therapy interventions may not be published in more readily accessible databases (Shekelle et al., 2005). Sources of grey literature searched for this review are shown in **Table 3**.

Table 3: Grey literature sources searched

Search #	Source (location/scope)
48	**Center for Research Literature** (CRL) (US/International)
49	**Embase** conference proceedings, preprint, conference papers (International)*
50	**British Library E-Theses Online Service (EThOS)** (UK)
51	**Open Access Theses and Dissertations (OATD)** (US/International)
52	**DART Europe E-theses Portal** (UK/Europe)

* included in PRISMA flow diagram under "databases and registers" papers with other Embase-retrieved papers

3.3.2.ii Hand-searching

Hand-searching of healthcare journals is recommended by the CHSRI to identify trials that may not have been indexed in bibliographic databases, or may have been indexed with terms not commonly used to identify trials (Lefebvre et al., 2022b).

Thirty English-language hand-searched journals were extracted from the Complementary Medicine Field of the Cochrane Register of Studies under the (Cochrane Collaboration, nd). This was augmented by a general internet search using Google (Google/Alphabet Inc., 2023) in February 2021 by entering all primary search terms from **Table 1** together with the words "journal", "publication" and "magazine" (separate searches). The first 20 results for each search were checked and details of 49 repositories were retrieved. Four were excluded as they were not published in languages included in this review; five were excluded as not relevant to the complementary therapies in this review. This resulted in 40 journals, making a list of 70 in total. These were checked in March 2023 against indexation lists for MEDLINE (National Library of Medicine, 2020b), Embase (Elsevier, 2023), and AMED (British Library, 2019). Twenty-seven were not indexed, and were individually investigated for relevance, accessibility and operational status. Fourteen met the criteria and were included in searches. **Table 4** shows the final list of sources that were hand-searched.

Table 4: Hand-searched sources

Search #	Source (location/scope)
53	**Bowen Studies and Research** (UK)
54	**Indian Journal of Ancient Medicine and Yoga** (India)
55	**Integrative Medicine: a Clinician's Journal** (US/International)
56	**International Journal of Kinesiology & Sports Science** (Australia/International)
57	**International Journal of Therapeutic Massage & Bodywork** (US/International)
58	**International Journal of Yoga** (India/International)
59	**Journal of Yoga Studies** (Vienna, Canada, UK/International)
60	**Journal of Yoga and Physical Therapy** (UK/International)
61	**Human Kinetics Journals** (US/International)
62	**Massage Therapy Journal** (US/International)
63	**Natural Medicine Journal** (US/International)
64	**Reflexology Research** (Canada/International)
65	**International Alliance of Healthcare Educators** (US/International)
66	**International Journal Of Alternative And Complementary Medicine** (US/International)

3.3.2.iii Citation searching

In addition to trials, the 66 searches listed above identified 82 broadly relevant reviews and commentaries, all of which were subjected to backward citation searching. Forward and backward citation searching was also carried out on the included studies (Lefebvre et al., 2022a).

Citation searching used the Google Scholar search engine (Google/Alphabet Inc., 2023); the process was logged and can be found in **Appendix E**, item 4. Although the ranking of results in Google Scholar is not transparent, thus limiting the reproducibility of the search, the engine may

identify more papers and citations in languages other than English (LOEs) than the Web of Science collections, which are explicitly constrained to English (Haddaway et al., 2015).

3.3.3 The search process

All searches were run 20-31 March 2023 and updated 18-27 October 2023. The update did not identify any new eligible studies.

No date, language or study type filters were used in the searches. Some interface-specific filters were used (for instance, where sources covered more than one type of complementary therapy and it was required to select a therapy to search).

Full details of the search strings, and their adaptations to each repository searched, can be found in **Appendix E**, items 2 and 5.

3.3.4 Review selection criteria

Selection criteria for the review are shown in **Table 5**.

Table 5: Review selection criteria

#	Inclusion	Exclusion
1	**Population:** Any form of current AF from any cause with any comorbidity	–
2	**Intervention:** Inclusion of at least one complementary therapy or element of complementary therapy as defined in lists above, applied as a monotherapy within one arm (or in addition to usual care/other therapy where this is also received by controls)	–
3	**Comparator:** Any	–
4	**Outcome:** At least one outcome related to change in existing AF symptoms (palpitations/tachycardia, dizziness, fatigue, breathlessness, chest pain, syncope, exercise intolerance, disordered sleep, depression) in the context of AF; or health-related quality of life in the context of AF	Prevention, secondary prevention or recurrence of AF Prevention, secondary prevention, recurrence or treatment of comorbidities or AF sequelae
5	**Study type:** Experimental/investigational studies	Animal studies Trial protocols or ongoing studies where results are not available Pilot/feasibility studies (unless including estimates of effect) Studies not available as English, Dutch or French full-text

3.3.5 Selection process

All screening and selection was carried out by the sole reviewer.

Results from the first eight bibliographic databases were imported into the review manager software Covidence (Veritas Health Innovation, 2023), where they were automatically de-duplicated. Title/abstract screening was prioritised using machine learning in Covidence, but all records were screened manually and no records were eliminated using automated methods. Full-text reports were retrieved and subjected to screening.

Results from all other sources were logged and screened manually using Microsoft Excel (Microsoft Corp., 2023); this log can be found in **Appendix E**, items 4 and 5.

Eight studies were identified and included from searches of the major bibliographic databases. Two studies were identified and included from backward citation searching of the 82 reviews identified in the searches. No studies were included from searches of websites or organisations.

Two studies had multiple reports:

- Lakkireddy et al., 2013 was supplemented by a conference abstract from 2011;
- Wahlström et al., 2017 was supplemented by conference abstracts from 2013 and 2018.

One study (Kodliwadmath et al., 2021) was included despite its single report being a conference abstract, as it reported almost all parameters necessary to conduct a representative risk of bias assessment.

One study (Wahlström et al., 2020) was a three-group trial of two interventions (yoga and relaxing music) versus standard care (control). In this review, only the yoga and control groups were included in data collection, analysis and synthesis.

3.3.6 PRISMA flow diagram

The full search and selection process is shown in the PRISMA flow diagram (**Figure 1**, overleaf).

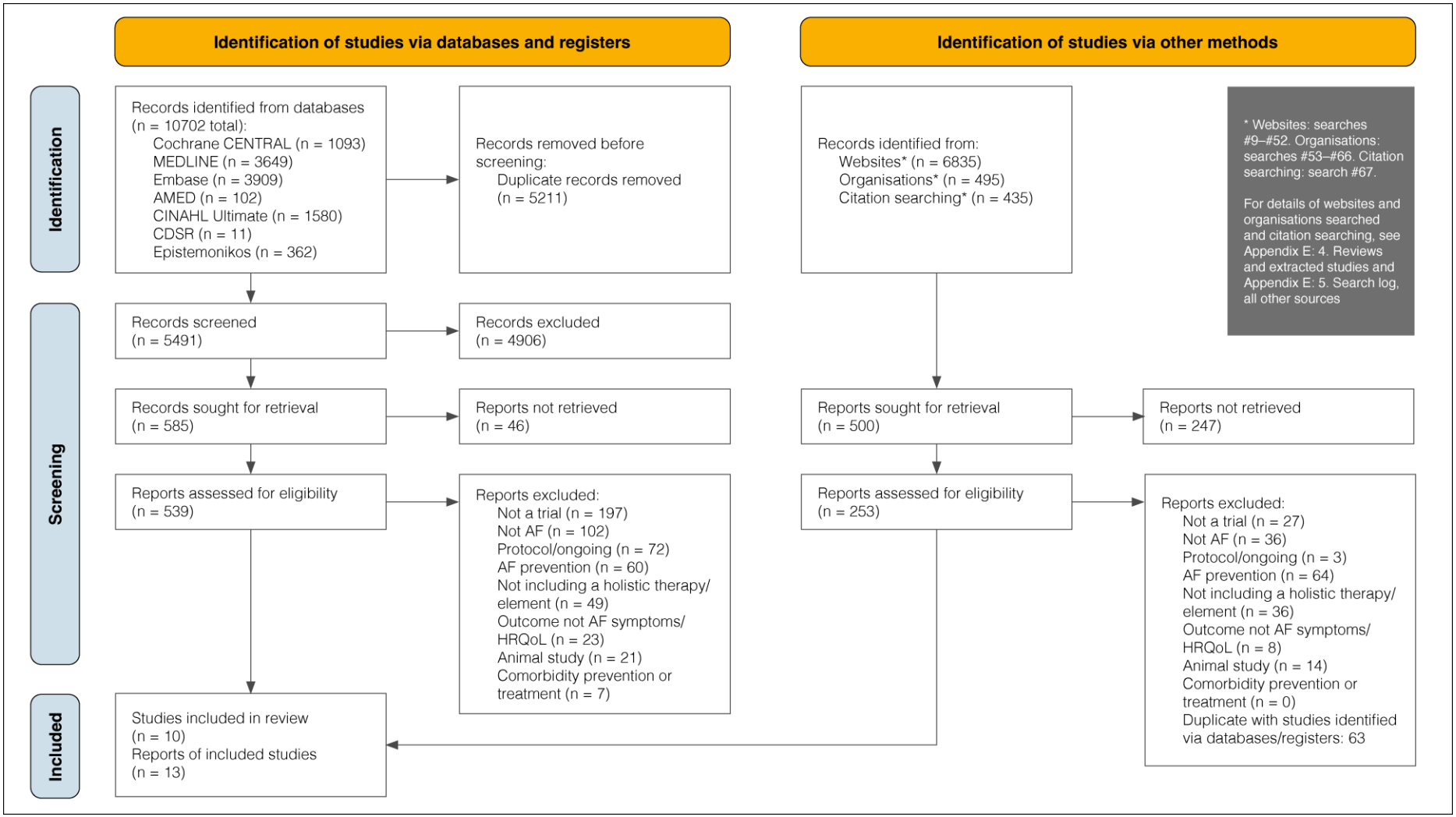

Figure 1: PRISMA flow diagram showing search and selection of studies

3.4 Data extraction and analysis of included studies

3.4.1 Characteristics of included studies

The 10 included studies represent four complementary therapies of the 18 searched for this review: four investigated yoga, three investigated Chinese herbal medicine, two investigated acupressure/acupuncture, and one investigated a dietary supplement. An effective total of 1,128 participants was included at baseline.

Of the 10 included studies, eight were randomised controlled trials, and two were non-randomised pre-post studies. These were included according to guidance in the CHSRI, suggesting that the inclusion of non-randomised studies is permissible when available randomised studies do not address the review question completely (Reeves et al., 2023), as in this review. The two non-randomised studies therefore provided evidence for acupuncture and yoga to help address the review question.

Data was extracted manually by the sole reviewer using a form designed in Microsoft Excel (Microsoft Corp., 2023). Extracted data included lead author and year of publication; participant numbers, randomisation, allocation concealment and blinding, where relevant; participants' AF and comorbidity characteristics including severity and duration; participants' current care regimes; intervention characteristics including dosage, timing, setting and mode of delivery; adherence, adverse events and length of follow-up; outcome measurement methods, instruments, and details reported; and reported statistics. Data was collected in an iterative process over the course of two weeks to minimise errors arising from the work of a sole reviewer (Barchard and Pace, 2011).

Table 6 (overleaf) shows the principal characteristics of the included studies, grouped by therapy type.

Table 6: Principal characteristics of included studies

#	Study name, year, type, country	N at baseline (intervention: control)	Setting, delivery	Population	Intervention	Comparator	Outcome: Symptoms	Outcome: HRQoL	Report of conflicts of interest / funding
ACUPUNCTURE / ACUPRESSURE									
1	Ceyhan et al., 2019 RCT, PC, PG Turkey	60 (30:30)	Hospital Administered by researcher	AF (type unspecified)	2/daily (over 2-4 days) + standard care	Sham acupressure (device used without applying pressure) + standard care	Heart rate (bpm), measured by constant ECG Fatigue, measured by BFI	n/a	No
6	Lombardi et al., 2012 NRPPS Italy	62 (31:31)*	Setting unspecified Mode of delivery unspecified	Paroxysmal AF with hypertension/ diabetes	1/7 days (once a week) over 10 weeks + anti-arrhythmic and/or rate control medication	No acupuncture + anti-arrhythmic and/or rate control medication	Total n episodes during post period and n minutes of symptomatic episodes, measured by self-report symptom diary	n/a	No
CHINESE HERBAL MEDICINE									
2	Deng et al., 2010 PG China	351 (223:128)	Hospital setting Intravenous delivery	AF (type unspecified) with hypertension, pulmonary or coronary heart disease, cardiomyopathy	1/daily intravenous Shenmai + intravenous amiodarone over 48h	Intravenous amiodarone only	n converting to NSR or showing reduced ventricular rate <100 times/min or >20% reduction from baseline, measured by ECG Time to conversion (minutes), measured by ECG	n/a	No
7	Meng et al., 2015 RCT, PG China	180 (91:89)	Hospital/ participants' homes Self-administered oral delivery	Paroxysmal AF and hyperthyroidism	3/daily oral Wenxin Keli over 3mo + methimazole + radiation therapy for 50% of group	Oral sotalol over 3mo + methimazole + radiation therapy for 50% of group	n converting to sinus rhythm, measured by ECG	n/a	Conflicts of interest only
10	Zhang et al., 2018 RCT, PG China	41 (20:21)	Hospital setting Self-administered Wenxin Keli	AF (type unspecified) with diabetes or hypertension	3/daily oral Wenxin Keli over 24 hours + intravenous amiodarone	Intravenous amiodarone only	n converting to NSR, measured by ECG Time to conversion (minutes), measured by ECG	n/a	Both

#	Study name, year, type, country	N at baseline (intervention: control)	Setting, delivery	Population	Intervention	Comparator	Outcome: Symptoms	Outcome: HRQoL	Report of conflicts of interest / funding
NUTRITION / SUPPLEMENTATION									
4	Kumar et al., 2013 RCT, PG Australia	78 (39:39)	Participants' homes Self-administered delivery	Paroxysmal AF or atrial tachycardia with hypertension, diabetes, heart disease, valvular disease, HF, LV hypertrophy	1/daily oral Omega-3 PUFAs over 6mo + standard care	Standard care only	n episodes/day and duration (hours), measured by pacemaker	n/a	Funding only
YOGA									
3	Kodliwadmath et al., 2021 RCT, PG, PC India	84 (42:42)	Setting unspecified / class size unspecified	Paroxysmal/ permanent AF	6/weekly sessions over 3mo + standard care	6 x joint exercise sessions daily (over 3mo) + standard care	Resting heart rate; heart rate after 6MWT, method unspecified Change in mEHRA/NYHA class (physician judged)	SF-36	Funding only
5	Lakkireddy et al., 2013 NRPPS USA	98 (49:49)*	Yoga studio Class size 15-20	Paroxysmal AF with coronary artery disease, diabetes, hypertension, hyperlipidaemia, OSA, revascularisation surgery	2 x Iyengar sessions/week over 3mo + encourage–ment to follow home practice + standard care	Standard care only during 3mo pre-period	n episodes/day, measured by self-report symptom diary and periodic cardiac monitor Heart rate, method unspecified Depression, measured by SDS	SF-36	Funding only
8	Wahlström et al., 2017 RCT, PG Sweden	80 (40:40)	Hospital physio-therapy clinic Class size maximum 10	Paroxysmal AF with hypertension, diabetes, stroke/TIA, ischaemic heart disease or heart failure	MediYoga (derived from Kundalini) for cardiac disease x 1/week over 3mo + standard care	Standard care only	Heart rate, measured by BP machine	Composite mental health & physical health scores of SF-36 and EQ-5D VAS	Both

#	Study name, year, type, country	N at baseline (intervention: control)	Setting, delivery	Population	Intervention	Comparator	Outcome: Symptoms	Outcome: HRQoL	Report of conflicts of interest / funding
YOGA									
9	Wahlström et al., 2020 RCT, PG Sweden	88 (44:44)	Hospital setting Class size unspecified	Paroxysmal AF with hypertension, stroke, MI, heart failure or OSA	MediYoga (derived from Kundalini) for cardiac disease x 1/week over 3mo + encouragement to follow home practice + standard care	Standard care only	Heart rate. Measured by BP machine after 5 mins' rest at 3mo follow-up	SF-36 and ASTA at baseline + 3mo	Both

* study is non-randomised pre-post study with single group. Pre-intervention period is given here as if parallel control group.

6MWT 6-minute walk test; **ASTA** Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia (Walfridsson et al., 2022); **BFI** Brief Fatigue Inventory; **BP** blood pressure; **ECG** electrocardiograph; **h** hours; **HF** heart failure; **LV** left ventricle; **mEHRA** modified European Heart Rhythm Association scale; **MI** myocardial infarction; **mo** months; **NRPPS** non-randomised pre-post study; **NSR** normal sinus rhythm; **NYHA** New York Heart Association scale; **OSA** obstructive sleep apnoea; **PC** placebo controlled; **PG** parallel group; **PUFAs** polyunsaturated fatty acids; **SDS** Zung self-rating depression scale; **SF-36** Short Form 36 questionnaire; **TIA** transient ischaemic attack; **VAS** visual analogue scale

3.4.2 Characteristics of excluded studies

Fourteen studies were screened but eventually excluded for not meeting eligibility criteria. Following the recommendations of Lefebvre et al. (2022a) these were tabulated, together with the reasons for their exclusion. This table can be found in **Appendix E**, item 8.

Four of these studies were excluded because the only reports were conference abstracts that did not give sufficient information to conduct a representative risk of bias assessment. Corresponding authors were emailed in March 2023 and again in November 2023. For the text of emails, see **Appendix E**, item 7. No responses were received.

3.4.3 Irretrievable records

The PRISMA flow diagram (**Figure 1**) shows that a high percentage of records sought from websites, organisations and citation searching could not be retrieved (n/N = 247/500, 49.4%). This compares with the records that could not be retrieved from searches of the eight major international bibliographic databases (n/N = 46/ 539, 8.5%).

Of the total 293 full-text records that could not be retrieved, 222 (75.8%) were published in domestic Chinese journals indexed by the Chinese databases CNKI and WanFang, and were not available in English full-text versions. These 222 articles investigated Chinese herbal medicines for the treatment of arrhythmias or AF (n=192), acupuncture for AF (n=13), or a combination of acupuncture and Chinese herbal medicines for the treatment of arrhythmias (n=17).

The number of records of Chinese studies screened may include some duplicates, which is a recognised issue in searching Chinese databases (Jia et al., 2020b; Tucker et al., 2011). In particular, where review authors have published in English but their included studies are only available in Chinese, titles may have been self-translated by review authors, resulting in slight title variations. Author teams appear to have published in multiple domestic journals, with some variations on the order of authors, and there also appears to be a degree of imprecision regarding publication year. All these features of Chinese citations have the effect of identifying apparently discrete studies which may in fact be identical. Clear duplicates were removed, but it was not possible to calculate how many remain.

Of the remaining 71 irretrievable records, 40 (13.7% of the original 293 irretrievable) were not available in this review's specified languages (English, Dutch, French). The remaining 31 (10.6%) could not be retrieved due to either (i) fees that could not be met within the resources of this study, or (ii) lack of record availability via the publisher's website or British Library Document Supply Centre holdings (usually for records published more than 25 years before these searches).

3.4.4 Risk of bias in included studies

Risk of bias (RoB) was assessed for all studies using Cochrane's RoB2.0 tool (Higgins et al., 2019). The design of the two pre-post studies was analogous to the randomised controlled trial premised by RoB2.0, and the signalling questions of RoB2.0 were therefore more applicable than those in the equivalent tool for non-randomised studies (the Cochrane Risk of Bias In Non-randomised Studies of Interventions (ROBINS-I) (Sterne et al., 2016)), which relates primarily to observational studies.

The RoB2.0 tool was applied by the sole reviewer, who recorded justifications for judgements of risk of bias in each domain (**Appendix E**, item 6). For the pre-post studies, the pre-intervention period was taken to be the control group, and the intervention period the intervention group; consideration was given to time-varying confounding (Sterne et al., 2016) that may have produced important differences between the two "groups" leading to a risk of bias in the outcomes assessed. An overall summary judgement was derived for each study (**Figure 2**).

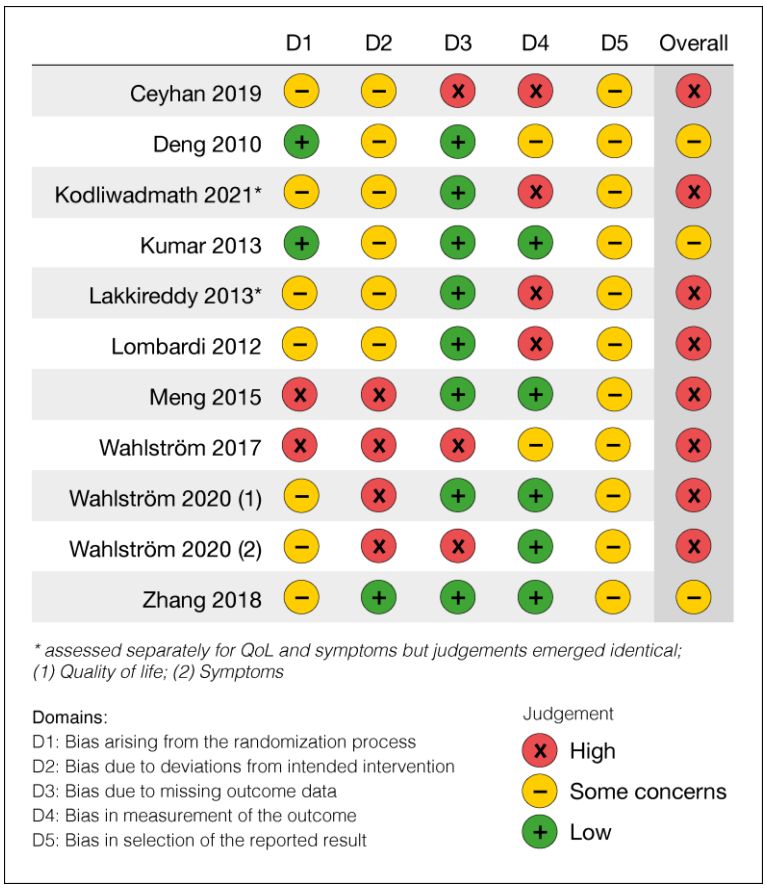

Figure 2: Cochrane Risk of Bias assessment for the included studies

3.4.5 Heterogeneity in included studies

Following recommendations set out by Gagnier et al. (2012), eight of the included studies (the randomised controlled trials) were investigated for clinical heterogeneity by tabulating dimensions of variability in characteristics of populations, interventions/settings and outcome measurements/methods. The included studies exhibited a high degree of clinical heterogeneity across three dimensions of the PICO model, described below.

3.4.5.i Heterogeneity of population

The populations in the included studies vary widely, with different types and durations of AF, a range of comorbidities, and varying medications. **Table 7** shows the range of population characteristics in the included studies.

Table 7: Clinical heterogeneity in populations of included studies

#	Study, intervention, location, type	Baseline characteristics and medications**	AF type; duration	Baseline comorbidities
ACUPUNCTURE/ACUPRESSURE				
1	Ceyhan 2019 Acupressure Turkey RCT, PC, PG	n=60 (30:30); 66.6% female μ age 63.7y CCB 61.6% Warfarin (n not specified)	Type/duration unspecified	"Another chronic disease/disorder" 75.0% Diabetes (unspecified number) Heart disease 51.6% Overweight/obese 45.0%
6	Lombardi 2012 Acupuncture Italy NRPPS	n=62 (31:31)**; 45.0% female μ age 55.0y Amiodarone 10.0% Flecainide 23.0% Propiophenone 32.0% Sotalol 6.0% CCB 6.0%	Paroxysmal Duration 84.0mo (assume μ)	Diabetes 29.0% Hypertension 58.0%
CHINESE HERBAL MEDICINE				
2	Deng 2010 China CT, PG	n=351 (223:128); 42.7% female μ age 72.7y Medications not specified	Type/duration unspecified	Cardiomyopathy 0.8% CHD 19.0% Hypertension 27.4% PHD 9.4%
7	Meng 2015 China RCT, PG	n=180 (91:89); 45.6% female μ age 55.8y Medications not reported	Paroxysmal μ duration 50.4mo	Hyperthyroidism 100.0% No other comorbidities reported
10	Zhang 2018 China RCT, PG	n=41 (20:21); 56.0% female μ age 71.5y ACE-I/ARB* 63.4% Beta-blocker 56.0% CCB* 41.5% Digoxin* 14.6% Statin 75.6%	Type unspecified μ duration 3.4h (0.005mo) prior to treatment*	Diabetes* 29.3% Hypertension 70.7%

Table continued overleaf

NUTRITION/SUPPLEMENTATION				
4	Kumar 2013 Australia RCT, PG	n=78 (39:39); 48.7% female μ age 77.5y Amiodarone 9.0% Flecainide 3.8% Renin-angiotensin inhibitor 55.0% Sotalol 24.4% Statin 60.0%	Paroxysmal, including atrial tachycardia Duration unspecified	Diabetes 21.8% Heart disease, ischaemic 21.8% Heart disease, structural 44.9% Heart failure, systolic 9.0% Heart valve disease 12.8% Hypertension 71.8% Left ventricular hypertrophy 18.0%
YOGA				
3	Kodliwadmath 2021 India RCT, PC, PG	n=84 (42:42); 56.0% female μ age 50.6y Medications not specified	Permanent Duration unspecified	Rheumatic heart disease 47.6%
5	Lakkireddy 2013 USA NRPPS	n=98 (49:49)**; 53.0% female μ age 60.6y ACE-I/ARB 20.4% Anti-arrhythmics 77.6% Aspirin 57.1% Beta-blocker 63.3% Statin 32.7%	Paroxysmal μ duration 63.9mo	Coronary artery disease 18.4% Prior CABG or PCI 8.2% Diabetes 2.0% Hyperlipidaemia 40.8% Hypertension 38.8% OSA 22.4%
8	Wahlström 2017 Sweden RCT, PG	n=69 (33:36); 39.1% female* μ age 63.5y ACE-I 34.8%* Anti-arrhythmic 49.2%* Aspirin 31.9% Beta-blocker 82.6% CCB 30.4% Statin 33.3%* Warfarin 55.0%	Paroxysmal Duration unclear ("early or new diagnosis"	Diabetes* 4.3% Heart disease, ischaemic 1.4% Heart failure 1.4% Hypertension* 47.9% Stroke/TIA* 7.2%
9	Wahlström 2020 Sweden RCT, PG	n=108 (38:41)*; 51.0% female μ age 64.0y Anti-arrhythmic* 40.0% Aspirin 5.5% Beta-blocker 68.0% CCB* 13.0% NOAC 44.4% Warfarin* 20.4%	Paroxysmal Duration unspecified	Heart failure* 0.9% Hypertension* 36.1% MI* 1.8% OSA 12.0% Stroke* 0.9%

* All variables evenly matched between groups unless noted with an asterisk

** study is non-randomised pre-post study with single group. Pre-intervention period is given here as if parallel control group.

ACE-I/ARB angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; **CABG** coronary artery bypass graft; **CCB** calcium channel blocker; **CHD** congenital heart disease; **NOAC** novel-acting oral anticoagulant; h hours; mo months; NRPPS non-randomised pre-post study; **PC** placebo control; **PCI** percutaneous coronary intervention; **PG** parallel group; **PHD** pulmonary heart disease; **TIA** transient ischaemic attack; **y** years

3.4.5.ii Heterogeneity of intervention and setting

Only four complementary therapies (of the 18 sought for this review) are represented in the included studies, but all cumulatively demonstrate a range of intervention-related clinical heterogeneity, including study setting and mode of delivery (**Table 8**, overleaf).

Table 8: Clinical heterogeneity in interventions and settings of included studies

#	Study, year, location, type	Intervention	Setting; delivery	Intervention dosage details
ACUPUNCTURE/ACUPRESSURE				
1	Ceyhan 2019 Turkey RCT, PC, PG	Acupressure + standard care**	Hospital (inpatients) Delivered by researcher, using two specially designed devices	2/daily x 5-minute acupressure sessions over 2-4 days on 2 bilateral acupoints on wrist + 1 unilateral acupoint on central sternum
6	Lombardi 2012 Italy NRPPS	Acupuncture + anti-arrhythmic and/or rate control medication	Setting not specified Delivery by unspecified personnel	1/7 days (once a week) x 15-20 minute treatments over 10 weeks using 3 x bilateral acupoints (2 on wrist + 1 on upper back)
CHINESE HERBAL MEDICINE				
2	Deng 2010 China CT, PG	Shenmai (Chinese herbal medicine) + amiodarone	Hospital (inpatients) Intravenous delivery by unspecified personnel	1/daily x 100ml intravenous injection + 150mg intravenous amiodarone over 48h
7	Meng 2015 China RCT, PG	Wenxin Keli (WK) + antithyroid medication + radiation therapy for 50% in intervention group; WK only for remainder. Unclear whether patients also received standard care**	Unclear, but infer outpatient for 50%; hospital inpatient + outpatients for 50% Self-administered by participants	3/daily x 18g oral over 3mo. 50% of intervention group also received methimazole 30mg/daily + radiation therapy 1x/30 days (once a month) over 3mo (unclear whether this 50% received both methimazole + radiation or just one)
10	Zhang 2018 China RCT, PG	Wenxin Keli (WK) + amiodarone	Hospital (inpatients) Self-administered by participants	3/daily x 18g oral over 24 hours + intravenous amiodarone 5mg/kg over 1 hour then 50mg/h for ≤24h
NUTRITION/SUPPLEMENTATION				
4	Kumar 2013 Australia RCT, PG	Omega-3 PUFAs + standard care**	Outpatient (participants' homes) Self-administered by participants	1/daily x 6g oral over 6mo (1.8g/day eicosapentaenoic acid + docosahexaenoic acid; remainder unspecified Omega-3 PUFAs)
YOGA				
3	Kodliwadmath 2021 India RCT, PC, PG	Yoga (tradition unspecified) + standard care ("guideline directed medical therapy")	Setting not specified Delivery by unspecified personnel Class size not specified	1/daily (6 days/week) x 60-minute yoga session over 3mo including movement, breathing and meditation
5	Lakkireddy 2013 USA NRPPS	Yoga (Iyengar) + standard care**	Yoga studio Delivery by unspecified personnel Class size 15-20	≥1/3.5 days (twice a week) x 60-minute yoga sessions over 3mo including meditation, movement, breathing, relaxation + support to practice independently at home using provided DVD
8	Wahlström 2017 Sweden RCT, PG	MediYoga for cardiac disease (derived from Kundalini) + standard care (medication, cardioversion, ablation)	Hospital physiotherapy clinic (outpatients) Delivery by experienced yoga instructor Class size maximum 10	1/7 days (once a week) x 60-minute sessions over 3mo including movement, breathing, meditation and relaxation + support to practice at home using provided CD/written instructions

Table continued overleaf

#	Study, year, location, type	Intervention	Setting; delivery	Intervention dosage details
9	Wahlström 2020 Sweden RCT, PG	MediYoga for cardiac disease (derived from Kundalini) + standard care (medication, cardioversion, ablation)	Hospital (outpatients) Delivery by trained MediYoga therapist Class size not specified	1/7 days (once a week) x 60-minute sessions over 3mo including movements, breathing, relaxation and meditation + support to practice at home using provided CD

* All variables evenly matched between groups unless noted with an asterisk ** No details specified for standard care

g grammes; h hours; **kg** kilogrammes; **mg** milligrammes; **mo** months; **PC** placebo control; **PG** parallel group; **PUFAs** polyunsaturated fatty acids

3.4.5.iii Heterogeneity of outcome

The included studies used a range of outcome measures and methods to measure HRQoL and symptoms, including self-reported, physician-judged and objective measures, a mix of binary and continuous outcomes, and widely varying follow-up length. **Table 9** shows the range of outcomes in the included studies; details of the intervention are given for context.

Table 9: Clinical heterogeneity in outcomes of included studies

#	Study, intervention, location, type	Intervention and control/comparator	Outcome measure and method (symptoms and HRQoL)	Length of follow-up
ACUPUNCTURE/ACUPRESSURE				
1	Ceyhan 2019 Turkey RCT, PC, PG	Acupressure + standard care** Sham acupressure + standard care**	Symptoms: Heart rate (bpm) measured by ECG (constant); fatigue measured by Brief Fatigue Inventory HRQoL: not measured	2/daily over 1-2 days dependent on length of hospital stay
6	Lombardi 2012 Italy NRPPS	Acupuncture + anti-arrhythmic and/or rate control medication No acupuncture (blanking period before intervention) + anti-arrhythmic and/or rate control medication	Symptoms: Total n AF episodes post-intervention period, measured by self-report symptom diary (count data) HRQoL: not measured	12mo
CHINESE HERBAL MEDICINE				
2	Deng 2010 China CT, PG	Shenmai (Chinese herbal medicine) + amiodarone Amiodarone alone	Symptoms: n converting to NSR within 48h or ventricular rate <100/min or reduction >20% compared with baseline (count) Time to conversion (minutes) measured by ECG HRQoL: not measured	Continuous monitoring over 48h
7	Meng 2015 China RCT, PG	Wenxin Keli (WK) (Chinese herbal medicine) + antithyroid medication + radiation therapy for 50% in intervention group; WK only for remainder** Sotalol + antithyroid medication + radiation therapy for 50% in control group; sotalol only for remainder**	Symptoms: n converting to NSR, measured by ECG (24h) or 12-lead ECG of unspecified duration (count data) HRQoL: not measured	3mo

#	Study, intervention, location, type	Intervention and control/comparator	Outcome measure and method (symptoms and HRQoL)	Length of follow-up
10	Zhang 2018 China RCT, PG	Wenxin Keli (WK) (Chinese herbal medicine) + intravenous amiodarone + standard care** Intravenous amiodarone + standard care**	Symptoms: n converting to NSR, measured by ECG (count data) Time to conversion (minutes), measured by ECG HRQoL: not measured	Continuous monitoring over 24h
NUTRITION/SUPPLEMENTATION				
4	Kumar 2013 Australia RCT, PG	Omega-3 poly-unsaturated fatty acids (PUFAs) + standard care** No Omega-3 PUFAs + standard care**	Symptoms: n AF episodes/day (count data) and duration (hours), measured by pacemaker HRQoL: not measured	6mo
YOGA				
3	Kodliwadmath 2021 India RCT, PC, PG	Yoga (tradition unspecified) + standard care Sham yoga (joint exercises) + standard care	Symptoms: Resting heart rate and heart rate after 6MWT (bpm) (method unspecified) Improvement in mEHRA/NYHA class (physician judged) HRQoL: SF-36	1mo, 3mo
5	Lakkireddy 2013 USA NRPPS	Yoga (Iyengar) + standard care** No yoga (blanking period before intervention)	Symptoms: n AF episodes/day, measured by self-report symptom diary and non-continuous cardiac monitor (count data) Heart rate (bpm), method unspecified Depression, measured by SDS HRQoL: SF-36	3mo
8	Wahlström 2017 Sweden RCT, PG	MediYoga for cardiac disease (derived from Kundalini) + standard care (specified as medication, cardioversion, ablation) Standard care only	Symptoms: Heart rate, measured by BP machine (bpm) HRQoL: SF-36 and EQ-5D	3mo
9	Wahlström 2020 Sweden RCT, PG	MediYoga for cardiac disease (derived from Kundalini) + standard care (specified as medication, cardioversion, ablation) Standard care only	Symptoms: Heart rate, measured by BP machine (bpm) HRQoL: SF-36 and ASTA	3mo

** No details specified for standard care

6MWT six-minute walk test; **ASTA** Arrhythmia-specific questionnaire in tachycardia and arrhythmia; **h** hours; **mEHRA** modified European Heart Rhythm Association scale; **mo** months; **NRPPS** non-randomised pre-post study; **NSR** normal sinus rhythm; **NYHA** New York Heart Association scale; **PC** placebo control; **PG** parallel group; **SDS** Zung self-rating depression score

3.4.6 Reporting quality of included studies

Reporting of the eight included randomised controlled trials was assessed using the CONSORT 2010 tool (Schulz, Altman and Moher, 2010). **Table 10** (overleaf) shows an overall summary of studies' reporting on the 37 individual items in the CONSORT checklist, including an overall level of reported and inapplicable items shown as a percentage of the total possible.

Reporting quality of the two non-randomised pre-post studies was not carried out, as no appropriate reporting guideline could be identified (EQUATOR Network, 2016).

Table 10: Reporting quality of included trials, using CONSORT 2010

#	Study	Not reported	Partially or unclearly reported	Reported	Not applicable	% CONSORT reported
1	Ceyhan 2019	10	13	8	6	37.8%
2	Deng 2010	17	6	9	5	37.8%
3	Kodliwadmath 2021	16	5	5	11	43.2%
4	Kumar 2013	8	8	16	5	56.8%
7	Meng 2015	10	13	8	6	37.8%
8	Wahlström 2017	9	11	10	7	45.9%
9	Wahlström 2020	6	12	12	7	51.4%
10	Zhang 2018	10	10	13	4	45.9%
	Aggregate %	**29.0%**	**26.4%**	**27.4%**	**17.2%**	

3.4.7 Bibliometric analysis of included studies

A bibliometric analysis was carried out to investigate the provenance of the included studies, using the journal metrics analysis service *Journal Citation Reports* (Clarivate PLC, 2023). The results are shown in **Table 11** (overleaf).

Table 11: Bibliometric features of included studies

#	Study	Journal	Publisher	Journal impact factor (IF)*	Language of publication**	Region of publication**
ACUPUNCTURE/ACUPRESSURE						
1	Ceyhan 2019	Alternative Therapies in Health and Medicine	InnoVision Professional Media	1.5	English	USA
6	Lombardi 2012	World Journal of Cardiology	Baishideng Publishing Group	1.8	English	USA
CHINESE HERBAL MEDICINE						
2	Deng 2010	Chinese Journal of Integrative Medicine	Springer	2.8	English	China mainland
7	Meng 2015	Evidence-Based Complementary and Alternative Medicine	Hindawi Ltd	2.4	English	England
10	Zhang 2018	Cardiology Research and Practice	Hindawi Ltd	2.1	English	USA
NUTRITION/SUPPLEMENTATION						
4	Kumar 2013	International Journal of Cardiology	Elsevier Ireland	3.3	English	Ireland
YOGA						
3	Kodliwadmath 2021	European Heart Journal (Supplements)	Oxford Academic	1.6	English	England
5	Lakkireddy 2013	Journal of the American College of Cardiology	Elsevier Science Inc.	23.5	English	USA
8 9	Wahlström 2017 and Wahlström 2020	European Journal of Cardiovascular Nursing	Oxford University Press	2.6	English	England

* taken from *Journal Citation Reports* for 2022, without self-citations (Clarivate PLC, 2023). ** taken from *Journal Citation Reports* for 2022

3.5 Synthesis

Meta-analysis was judged inadvisable due to the degree of clinical heterogeneity and concerns about bias in the included studies; the combination of these factors indicated that statistical synthesis of any kind would produce misleading evidence of the effect of complementary therapies for symptoms or HRQoL in AF (Campbell et al., 2020). This review had planned to investigate statistical heterogeneity using Cochran's Q test and the I^2 index (Sedgwick, 2015; Higgins, 2008); however, the small number of studies identified for each therapy meant that the I^2 statistic would be subject to bias and therefore not a useful metric (von Hippel, 2015).

Other types of statistical synthesis were explored, grouping by therapy and by outcome type. Studies that reported medians and interquartile ranges for between-group continuous data differences at follow-up were assumed to be non-normal unknown distributions and were investigated for conversion to mean and standard deviation (McGrath et al., 2020). Sensitivity

analyses were planned to isolate the effects of studies judged to be at low risk of bias. However, clinical heterogeneity, coupled with high or "some concerns" risks of bias for all studies, and reporting omissions that did not allow extraction or conversion of a standardised metric to pool intervention effects by any method judged "acceptable" (McKenzie and Brennan, 2022), meant that statistical synthesis was both impractical and inadvisable.

Following the guidance set out by Popay et al. (2006) and Rodgers et al. (2009), a narrative approach to synthesis was appropriate for this review (Chaimani et al., 2022; McKenzie et al., 2022). Studies were grouped for synthesis firstly by outcome domain (symptoms, HRQoL), within which they were grouped by therapy and ordered by direction of effect. A third grouping describes the safety of all included studies. All three groupings represent the outcomes of most importance to people with AF (Seligman et al., 2020).

3.5.1 Symptoms

All 10 studies (n=1,128 participants at baseline) included at least one measure of symptomaticity and were included in the narrative synthesis addressing the question "What is the effect of complementary therapies on symptoms in AF?". For a summary of the key PICO characteristics of these 10 studies, see **Table 6**.

Of a total 21 symptomaticity measures across the 10 studies,18 favoured the intervention (2,027 (92.3%) observations), two showed no effect of the intervention (108 (4.9%) observations) and one favoured the control (60 (2.7%) observations). Three studies, with a total of six symptomaticity measures, were judged to be at "some concerns" risk of bias for the Symptoms domain; five of these measures favoured the intervention, while the remaining one measure showed no effect of the intervention. The remaining seven studies, with a total of 15 symptomaticity measures, were judged to be at high risk of bias for the Symptoms domain; 13 of these measures favoured the intervention, while the remaining two measures showed no effect or favoured the control.

3.5.1.i Outcome statistics, Symptoms domain

Reported outcome statistics for the Symptoms domain are shown in **Table 12**, overleaf. All statistics were derived from the primary report (journal article) for each study.

Table 12: Outcome statistics for Symptoms domain

#	Study	Outcome (measurement)	Intervention n/N Control n/N	Group values at follow-up	Direction of effect
ACUPUNCTURE/ACUPRESSURE					
1	Ceyhan 2019 Acupressure	Heart rate, bpm (constant ECG) at 48h [2]	20/30 18/30	73.5 (67.0–85.5)* 79.0 (72.7–86.2)*	Favours intervention
1a		General fatigue (BFI) at 48h [2]	30/30 30/30	39.0 (18.5–53.5)* 40.0 (9.7–64.2)*	Favours intervention
1b		Activity fatigue (BFI) at 48h [2]	30/30 30/30	27.0 (8.5–37.7)* 27.5 (5.0–43.5)*	Favours control
6	Lombardi 2012 Acupuncture	Total n episodes during 12mo post period (symptom diary) [2]	31/31 [5] 31/31 [5]	2.0 (1.0–10.0)* 15.0 (6.0–50.0)*	Favours intervention
6a		n minutes symptomatic episodes (symptom diary) [2]	31/31 [5] 31/31 [5]	6.0 (1.0–20.0)* 100.0 (30.0–180.0)*	Favours intervention
CHINESE HERBAL MEDICINE					
2	Deng 2010 Chinese herbs	n converting to NSR within 48h (ECG) [1]	223/223 128/128	170.0 (76.0%) 89.6 (70.0%)	Favours intervention
2a		Time to NSR conversion, minutes (constant ECG) [2]	223/223 128/128	351.0±123.0 570.0±211.0	Favours intervention
2b		Ventricular rate, times/min (<100 times/minute or decrease of >20% on baseline) within 48h (ECG) [2 4]	223/223 128/128	91.8 101.6	Favours intervention
7	Meng 2015 Chinese herbal medicine	n converted to NSR at 3mo (24h ECG or 12-lead ECG, duration unspecified) [1]	91/91 89/89	83 (91.2%) 80 (89.9%)	Favours intervention
10	Zhang 2018 Chinese herbs	n converted to NSR (constant ECG) at 24h [1]	21/21 20/20	16 (75.0%) 16 (81.0%)	No effect
10a		Time to NSR conversion, minutes (constant ECG) [2]	21/21 20/20	291.0±235.0 725.0±475.0	Favours intervention
NUTRITION/SUPPLEMENTATION					
4	Kumar 2013 Nutrition / supplement	Average n episodes/day during 6mo period (pacemaker) [2]	39/39 39/39	0.4 (0.1–4.4)* 0.8 (0.1–4.7)*	Favours intervention
4a		Average episode duration (h) during 6mo period (pacemaker) [2]	39/39 39/39	0.3 (0.0–2.1)* 0.9 (0.1–3.3)*	Favours intervention
YOGA					
3	Kodliwadmath 2021 Yoga	Change in resting heart rate, bpm at 3mo vs. baseline (method unspecified) [1 3]	38/42 39/42	10.0±10.24 1.1±9.63	Favours intervention
3a		Change in heart rate after 6MWT, bpm at 3mo vs. baseline (method unspecified) [1 3]	38/42 39/42	11.5±10.6 0.8±10.0	Favours intervention

Table continued overleaf

#	Study	Outcome (measurement)	Intervention n/N Control n/N	Group values at follow-up	Direction of effect
5	Lakkireddy 2013 Yoga	Average n symptomatic episodes/day (symptom diary + cardiac monitor) [2]	49/49 [5] 49/49 [5]	2.1±2.6 3.8±3.0	Favours intervention
5a		Depression (SDS) at 3mo [2]	49/49 [5] 49/49 [5]	27.0 (22.0–31.0)* 29.0 (24.0–35.0)*	Favours intervention
5b		Heart rate (unspecified method) at 3mo [2]	49/49 [5] 49/49 [5]	61.5±7.6 64.7±7.5	Favours intervention
8	Wahlström 2017 Yoga	Heart rate at 3mo (BP machine) [2]	33/40 36/40	61.0±13.0 70.0±19.0	Favours intervention
9	Wahlström 2020 Yoga	Heart rate at 3mo (BP machine) [2]	38/44 41/44	58.0±8.0 58.0±7.0	No effect (intervention vs. control)
9a		ASTA Symptoms at 3mo [2]	38/44 41/44	27.0±18.0 30.0±16.0	Favours intervention

* Median (interquartile range); otherwise mean ± standard deviation

[1] higher numbers better; [2] lower numbers better; [3] within-group change figure only reported; [4] count data only reported; [5] pre-post study (participants were their own controls) – top figure post-intervention ("intervention"), bottom figure pre-intervention ("control")

6MWT 6-minute walk test; **ASTA** Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia; **BFI** Brief Fatigue Inventory; **bpm** beats/minute; **h** hours; **NSR** normal sinus rhythm; **SDS** Zung self-rating depression score

3.5.1.ii Visual representation of outcome statistics, Symptoms domain

A harvest plot (Ogilvie et al., 2008) was used to visually represent the synthesis of the Symptoms domain outcome statistics (**Figure 3**, overleaf). In the plot, studies' shade shows therapy type; height represents risk of bias. Each bar shows the study, symptom measurement and length of follow-up, with the number of observations for that measure in the study. Outcomes are grouped according to therapy (shade) and direction of effect (location on the x-axis).

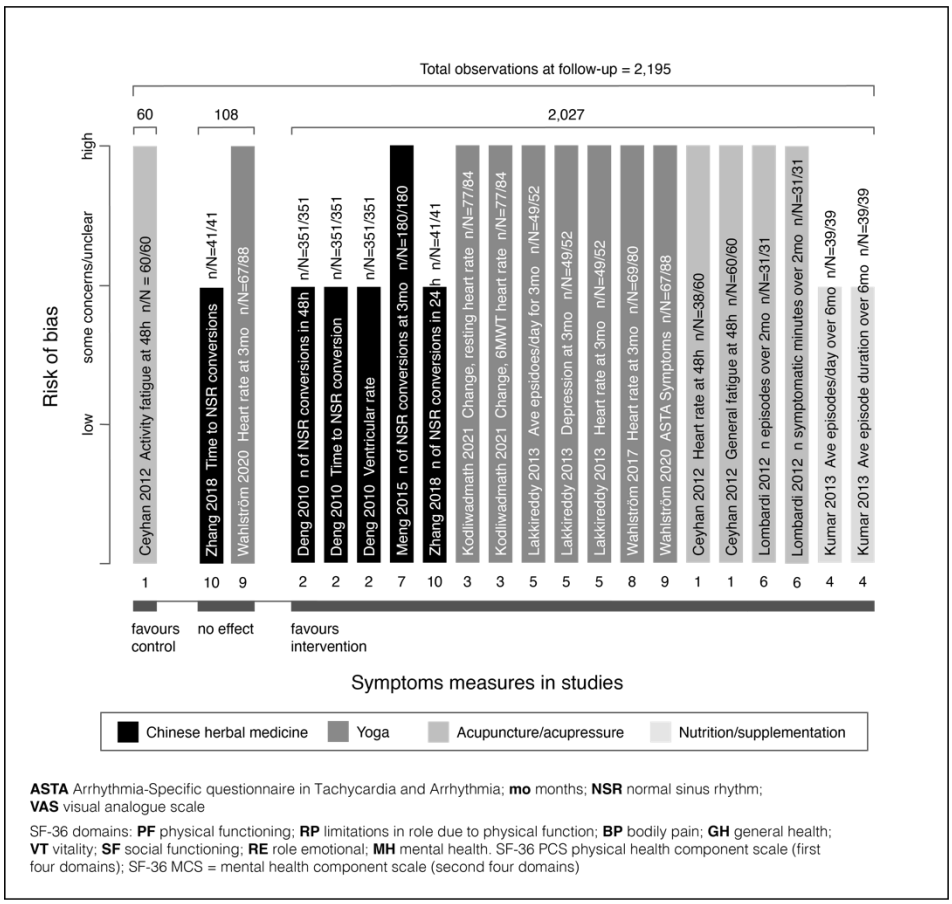

Figure 3: Harvest plot showing direction of effect for Symptoms domain

3.5.2 Quality of life

Four studies (n=304 participants at baseline) included at least one quality of life measure and were included in the narrative synthesis addressing the question "What is the effect of complementary therapies on HRQoL in AF?". All were yoga studies; for a summary of the key PICO characteristics, see **Table 6**.

Of a total 28 HRQoL measures across the four studies, 25 favoured the intervention (1,627 (88.3%) observations), one showed no effect of the intervention (69 (3.7%) observations) and two favoured the control (146 (7.9%) observations). All studies were judged to be at high risk of bias for the HRQoL domain.

3.5.2.i Outcome statistics, HRQoL domain

Outcome statistics for the HRQoL domain are shown in **Table 13**. All statistics were derived from the primary report (journal article) for each study.

Table 13: Outcome statistics for HRQoL domain

#	Study	Measure + follow-up length)	Intervention n/N Control n/N	GROUP VALUES AT FOLLOW-UP Intervention	 Control	Direction of effect
YOGA						
3	Kodliwadmath 2021 Yoga	SF-36 at 3mo [1 3 4]	38/42 [4] 39/42 [4]	PF: 15.2 [3] RP: 7.2 [3] BP: 1.6 [3] GH: 13.2 [3] VT: 11.2 [3] SF: 8.5 [3] RE: 5.0 [3] MH: 7.5 [3]	-2.5 [3] -1.4 [3] 7.4 [3] 10.0 [3] 4.8 [3] 4.6 [3] -2.5 [3] 2.9 [3]	7 favour intervention 1 favours control
5	Lakkireddy 2013 Yoga	SF-36 at 3mo [1 4]	52/52 [5] 52/52 [5]	PF: 90.0 (85.0–95.0)* RP: 100.0 (86.3–100.0)* BP: 100.0 (100.0–100.0)* GH: 75.0 (65.0–82.5)* VT: 91.0 (80.0–95.8)* SF: 100.0 (90.0–100.0)* RE: 78.0 (60.5–80.0)* MH: 80.0 (70.0–86.0)*	85.0 (70.0–93.8)* 100.0 (56.3–100.0)* 100.0 (100.0–100.0)* 60.0 (45.0–75.0)* 84.0 (73.0–91.0)* 100.0 (75.0–100.0)* 68.0 (58.5–80.0)* 75.0 (65.0–80.0)*	Favours intervention
8	Wahlström 2017 Yoga	EQ-5D VAS at 3mo [1]	33/40 36/40	80.0 (50.0–100.0)*	80.0 (30.0–95.0)*	No effect
		SF-36 MCS at 3mo [1 6]	33/40 36/40	50.6 (24.0–55.2)*	52.7 (24.5–57.1)*	Favours control
		SF-36 PCS at 3mo [1 6]	33/40 36/40	50.2 (27.6–59.1)*	49.0 (29.1–61.6)*	Favours intervention
9	Wahlström 2020 Yoga	SF-36 at 3mo [1 4]	38/44 41/44	PF: 86.0±14.0 RP: 68.0±40.0 BP: 83.0±19.0 GH: 70.0±17.0 VT: 61.0±17.0 SF: 88.0±18.0 RE: 77.0±35.0 MH: 72.0±16.0	85.0±14.0 58.0±43.0 76.0±23.0 65.0±21.0 57.0±16.0 83.0±19.0 66.0±40.0 67.0±13.0	Favours intervention
		ASTA QoL at 3mo [2]	38/44 41/44	21.0±17.0	25.0±18.0	Favours intervention

* Median (interquartile range), otherwise mean ± standard deviation

[1] higher numbers better; [2] lower numbers better; [3] within-group change figure only reported; [4] scores for eight individual SF-36 domains reported in order: **PF** physical functioning, **RP** limitations in role due to physical function, **BP** bodily pain, **GH** general health, **VT** vitality, **SF** social functioning, **RE** role emotional, **MH** mental health; [5] pre-post study (participants were their own controls) – top figure post-intervention ("intervention"), bottom figure pre-intervention ("control"); [6] only composite scores for mental health domains (MCS) and physical health domains (PCS) reported

ASTA Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia; **mo** months

3.5.2.ii Visual representation of Quality of life domain summary statistics

A harvest plot (Ogilvie et al., 2008) was used to represent the synthesis of the Quality of life domain data visually (**Figure 4**). In the plot, studies' shade shows type of therapy (all yoga studies), and height represents risk of bias (high for all measures). Each bar shows the study, HRQoL measurement and length of follow-up, with the number of observations for that measure in the study. Measurements are grouped according to their direction of effect.

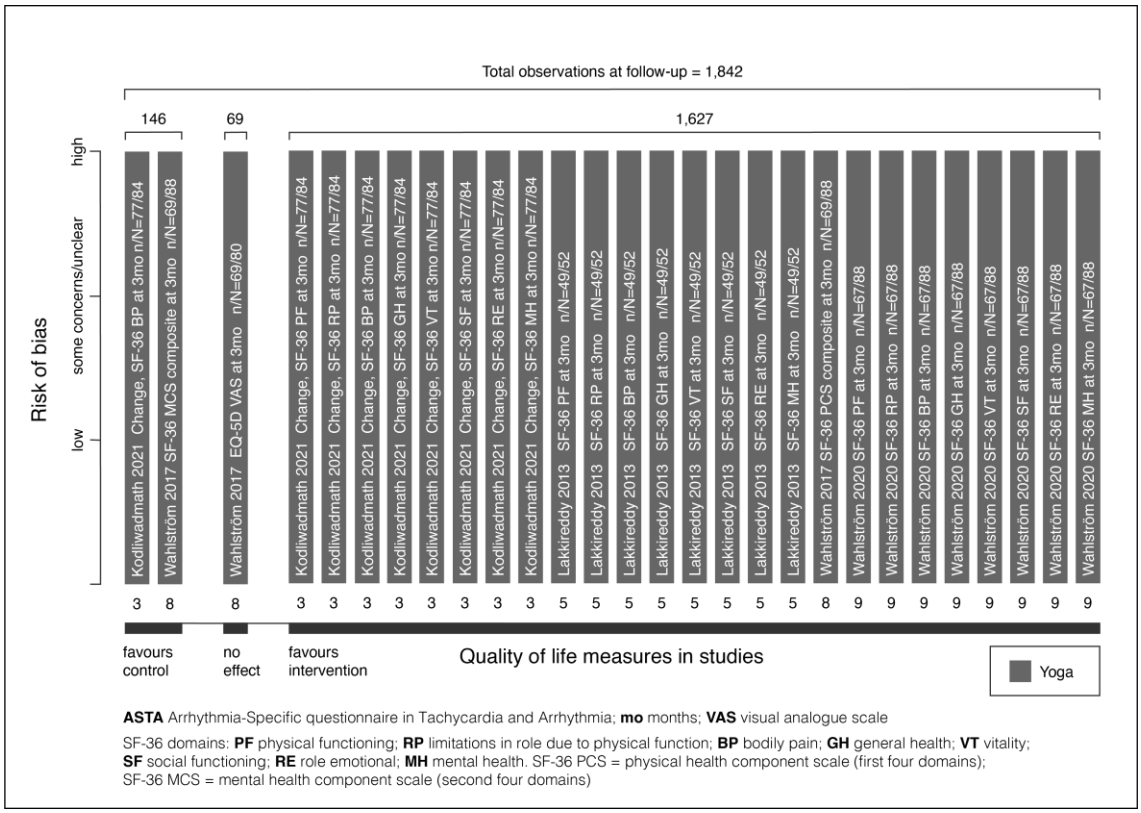

Figure 4: Harvest plot showing direction of effect for Quality of life domain

3.5.3 Safety

Of the total 10 included studies (1,128 participants at baseline), eight (n=877 participants, 77.7%) included some description of adverse events or safety, and were included in this narrative summary addressing the question "What is the safety of complementary therapies for atrial fibrillation?". For a summary of the key PICO characteristics of these studies, see **Table 6**.

Of the eight reporting studies (960 participants), five studies reported no harms (268 (27.9%) participants), while four studies (609 (63.4%) participants) reported a range of harms affecting an overall 37 participants (3.9%). Two studies did not report on harms (Wahlström 2017 and Wahlström 2020). Data is shown in **Table 14** (overleaf).

Table 14: Safety of complementary therapies for atrial fibrillation

	Participants in study		Number of participants affected			
	Report of no harms	Report of harms	Hypo-tension	GI symptoms inc nausea, vomiting, dizziness, bloating, fishy eructation	More severe symptoms leading to dose reduction	Ceased therapy altogether
Ceyhan 2019	60	–	Report of no harms			
Deng 2010	–	351	9	4	–	–
Kodliwadmath 2021	84	–	Report of no harms			
Kumar 2013	–	78	–	7	6	1
Lakkireddy 2013	52	–	Report of no harms			
Lombardi 2012	31	–	Report of no harms			
Meng 2015	–	180	–	10	–	–
Zhang 2018	41	–	Report of no harms			
Total participants (% of pooled study population)	268 (23.8)	609 (54.0)	9 (0.8)	21 (1.9)	6 (0.5)	1 (0.1)

GI gastro-intestinal

3.6 Discussion

3.6.1 Clinical and methodological heterogeneity

The included studies are notable for a combination of clinical heterogeneity in the dimensions of study population, intervention, setting and outcome measures; methodological heterogeneity in the form of poor methodological quality; and poor reporting (the latter two being interconnected). As a result, Grading of Recommendations, Assessment, Development and Evaluation (GRADE) (Schünemann et al., 2013; Guyatt et al., 2008) was not applied because PICOs were not sufficiently similar between studies to construct meaningful Summary of Findings tables for each outcome domain.

These factors are critically discussed below in relation to this review.

3.6.1.i Clinical heterogeneity in the included studies

The clinical heterogeneity apparent in Tables 7–9 is extensive, and identifies several important modifiers of effect in the study of therapeutic interventions for AF (Popay et al., 2006). **Table 7** shows the diverse range of population characteristics in the included studies. While randomisation may be assumed to balance the effects of varying population characteristics between individual studies' groups, the widely differing population characteristics between studies made effect pooling inadvisable. For example, there is a wide variation in mean duration of AF (3.4 hours–84.0 months)

while five studies (50%) do not report AF duration at all. As discussed in **2.1.4.i**, the length of AF diagnosis may correspond to the extent of cardiomyopathy and atrial remodelling, resulting in a greater or lesser degree of refractoriness that was not addressed in any of this review's included studies. Equally, no study reports changes in the standard care to which most therapies were adjunctive, although some studies excluded patients with recent or imminent change, or noted that participants' medical therapy was "stable" throughout the study (Lakkireddy et al., 2013, p.1178).

Another instance of heterogeneity shown in **Table 7** is the number of comorbidities in studies' populations, which again may contribute to cardiomyopathy and remodelling, obscuring the true effects of treatments. Some studies (Kumar 2013; Ceyhan 2019) include participants with more than one comorbidity, but the numbers of patients with comorbidities (and which) are not reported; in addition, no study reported on the duration of any comorbidity except Ceyhan's note that proportions of the intervention and control groups had been diagnosed with "heart disease" (not defined) for 0-5 years. Some studies report only selected comorbidities: for instance, the medications listed by Zhang 2018 suggest that the reported diabetes and hypertension are not the only comorbidities in the study population, while Deng 2010 reports only cardiac comorbidities and Meng 2015 only hyperthyroidism.

Given the close relationship between AF and a number of comorbidities, the detailed reporting of comorbidities and length of AF diagnosis is important for future trials and reviews of therapeutic interventions for AF. Had more studies of a single, sufficiently homogeneous complementary therapy been identified for this review, and had length of AF diagnosis and comorbidities been adequately reported, it would have been interesting to undertake sensitivity analyses to detect any associations between various combinations of comorbidities, durations of AF and/or comorbidity diagnosis, and therapeutic outcomes. AF researchers are beginning to identify the importance of reporting the extent of comorbidity and AF duration and including this in analyses; for instance, in a recent cohort study, Hu et al. (2021) found that a protective effect of acupuncture was "more obvious for those with fewer comorbidities" (p.1). This review was not able to include sufficient studies to investigate this proposition, but even its small number of studies broadly align with Hu's findings. For instance, it can be observed that Zhang 2018, providing oral Chinese herbal medicine to a population with AF onset measured in hours and only two (reported) comorbidities of diabetes and hypertension, achieved a 75% conversion rate to normal sinus rhythm within 24 hours; this compares with, say, Lakkireddy 2013, providing twice-weekly yoga to a population with AF onset of mean duration 64 months with at least one of six comorbidities including coronary artery disease and prior revascularisation surgery, achieving a more moderate between-groups reduction in daily symptomatic episodes of 1.7 after three months. Clinical heterogeneity makes the comparison unsound, but the principle is clear: these effect modifiers could be useful in understanding the effect of interventions for AF if controlled for in analyses.

Table 8 describes the heterogeneity evident within each therapy type, including the setting of therapy delivery: even where therapies are identical, the setting, the mode of administration and dosage vary widely. For instance, the three studies of two different Chinese herbs (Deng 2010, Meng 2015 and Zhang 2018) are delivered in hospital inpatient/outpatient settings, orally and intravenously, using intensive 24-48h dosing and/or ongoing dosing in the community; this diversity is also clear in the two studies that use acupuncture principles, which are again delivered in a combination of hospital inpatient and outpatient settings, over four days or 10 weeks. Differences in setting and delivery give rise to a substantial difference in potential for the effect of both specific and non-specific effects associated with each therapy (Bishop et al., 2021; MacPherson and Charlesworth, 2020; Paterson and Dieppe, 2005); the originally planned grouping for synthesis by therapy type was not able to neutralise this within-therapy heterogeneity.

Further, the generalisability of the settings and modes of administration in this review is questionable. Only one study delivered its therapy in a setting and manner representative of routine practice (Lakkireddy 2013, yoga studio); conversely, most hospitals outside China would not administer intravenous Chinese herbs to inpatients with acute atrial fibrillation (Deng 2010), and it is also unlikely that a registered Chinese herbalist would use this mode of administration.

Table 9 shows the extent of heterogeneity of outcome measurement instruments and methods. The main types of data are continuous and time-to-event, but differing lengths of follow-up combined with poor reporting made it difficult to extract a meaningful standardised metric; this aligns with the findings of Qiu et al. (2019) who found wide variation in outcomes, measurement instruments and follow-up durations in AF studies. For instance, the six studies measuring heart rate (1 acupressure, 1 Chinese herbal medicine, four yoga) did so over follow-up periods between 24 hours and three months, and some did not describe measurement methods. This heterogeneity, coupled with a lack of reporting on assessor blinding, suggests at least the potential for bias. For instance, if heart rate was measured using automated methods and assessors were blinded to the intervention received, this could be viewed as an objective measure and therefore relatively free from risk of bias; but if heart rate was measured by an unblinded assessor using the traditional radial artery palpation method, heart rate becomes a subjective measure with a higher risk of bias.

Four yoga studies measured HRQoL using the SF-36 questionnaire (RAND Corporation, 2023) over a three-month period, but none reported this using a metric that could be standardised for the others (Kodliwadmath 2021 reported within-group change; Lakkireddy reported a *p*-value for pre-post change; Wahlström 2017 reported only the composite SF-36 scores at follow-up; Wahlström 2020 was a three-group trial reporting a single *p*-value for between-groups change without specifying which two groups had been included in the analysis). No authors responded to queries sent in March and November 2023.

The effect of clinical heterogeneity across the above dimensions was a judgement that outcome pooling between studies (even given identical therapy type) would be likely to misrepresent the effects of the therapy in the treatment of AF, and mislead decision-makers. However, this investigation of heterogeneity has usefully identified a number of effect modifiers (Popay et al., 2006) that are recommended as covariates in the analysis of future trials and systematic reviews in the area of AF.

3.6.1.ii Methodological heterogeneity and poor reporting in the included studies

Methodological heterogeneity in a systematic review typically comprises variability between the included studies in the dimensions of study design and quality (Gagnier et al., 2012).

The two included non-randomised pre-post studies add an obvious element of methodological heterogeneity in the dimension of study design. While it could be argued that the review would have produced more reliable evidence had all studies been homogenous in this dimension (i.e., all randomised controlled trials) (Peinemann, Tushabe and Kleijnen, 2013), there were overriding concerns about the quality of the included studies that were likely to substantially prejudice this review's strength of evidence in any case. In addition, all included studies exhibited a degree of clinical heterogeneity that made statistical synthesis inadvisable; in view of these factors, achieving homogeneity in one dimension was thought to be irrelevant. Instead, the two non-randomised studies were included in order to illustrate a breadth of evidence in response to the review's research question, justified by the CHSRI's guidance on including studies of other designs in cases where a question cannot be answered due to insufficient evidence when using a single study design (Lefebvre et al., 2022a). However, it should be noted that, in synthesising the direction of effect for these two studies, the blanking period at the start of each was counted as a control group, and the subsequent intervention period as an intervention group; the potential biases of this approach are well-documented, including regression to the mean effects, test-retest validity, and simple temporal effects (Ho et al., 2019; Torgerson and Torgerson, 2008). To this extent, the inclusion of these two studies must be regarded as further weakening the reliability of evidence provided by this review.

The quality of included studies was a significant concern. While a formal quality appraisal was not carried out for each included study, there was a pervasive absence of methodological safeguards against bias in the design, conduct and analysis of most of the included studies (Furuya-Kanamori et al., 2021), and risk of bias assessment correspondingly resulted in either high or "some concerns" judgements for all studies. Examples of poor study quality include, for instance, the fact that all trials appear to have been opportunistic (typically "all the 351 AF patients who visited our hospital from July 2006 to June 2009 were chosen" (Deng et al., 2010, p.453)); additionally, no study reported a sample size calculation or a target effect size, without which it is not possible to

understand whether studies were adequately powered to detect an appropriate target difference at follow-up.

Choice of comparator/control was another area of methodological weakness in the included studies: while most controls were clinically congruent with their equivalent intervention, there is a strong possibility that some may not have been inert (most obviously Kodliwadmath's joint exercises as a yoga control, and Ceyhan's sham (non-pressure) acupressure). The choice of a potentially non-inert control may obscure treatment effects (Vickers et al., 2018; Benedetti and Dogue, 2015; MacPherson et al., 2014) which, coupled with small sample sizes, suggests a strong risk of bias (favouring the control) for these two studies.

Another example of poor study quality was the blinding of outcomes assessors, which was not described in any study (although Kumar 2013 made passing reference to the retrieval of pacemaker data "in an un-blinded fashion" (p.3814)). As participants for the most part were aware of their allocation, and most studies used at least one self-report outcome in which the outcomes assessor is considered to be the participant themselves (Higgins et al., 2019), it may be that study authors considered blinding redundant. However, the joint effect of lack of blinding and the use of subjective outcomes was to increase the risk of bias.

Two studies appear to favour the intervention by design. Deng 2010 and Zhang 2018 measured conversion to NSR over a period of 48 and 24 hours respectively, a period in which regression to the mean occurs at a high rate (Pluymaekers et al., 2019); while the sample size of Deng et al. (n=351) offers grounds for greater confidence in the result, the sample size of Zhang (n=41) does not.

Finally, no included study published a protocol; the single study to be entered in a clinical trials registry was Kumar 2013 (without an accompanying protocol). The effect of this was to render all trials at "some concerns" risk of bias in selection of the reported result simply because it was not possible to judge whether authors had manipulated the selection of their results without a protocol against which the study report could be compared (Roberts et al., 2015).

3.6.2 Bias in systematic reviews of complementary medicine

Bias in systematic reviews may arise from many sources, including eligibility criteria, identification and selection of studies, data collection and study appraisal, and synthesis (Whiting et al., 2016). For reviewers of complementary therapies, there is additional potential for bias arising from additional factors including obstacles to study retrieval, the difficulties of comparing CAM modalities with each other, and the variations in practice or formulation of apparently identical therapeutic strategies that make comparisons and the pooling of effects difficult (Cramer and Chung, 2016;

Wider and Boddy, 2009). This review may be considered subject to bias arising from all these issues.

Reviews of complementary therapies are likely to be particularly subject to bias arising from a combination of language and location biases in the publication of trials. Language and location bias – defined by the Cochrane Methods Bias Group as the association between nature/direction of results and, respectively, the language of publication and the ease of accessing the publication (Cochrane Bias Methods Group, 2022) – are particularly relevant in complementary therapy research, where the results of trials carried out in the "home" countries of complementary therapies are often highly positive in favour of the intervention, showing larger effects than those typically demonstrated by equivalent studies carried out in countries or regions to which the therapy is not indigenous (Chen et al., 2015; Vickers et al., 1998).

Together, language and location biases contribute to overall publication bias (Tangkiatkumjai, 2017), the effects of which may exist in this review. Of a total 49 separate outcomes measured in the included studies, 43 favoured the intervention, three showed no effect and three showed a negative effect. This suggests the possibility of publication bias at the level of the included studies – in this case, the specific form of publication bias in which the direction of the results influences the likelihood of publication (Cochrane Methods: Bias, 2023). Aggregated, the included studies may confer bias on this review if they differ systematically from studies which were either not published or not retrievable by this review. Publication bias could not be reliably demonstrated in this review, since most of the studies did not report the statistics needed for analysis, and the small number of studies would not produce a reliable result (Song, Hooper and Loke, 2013).

This review attempted to mitigate the possibility of publication bias by searching extensively and including sources recommended to mitigate publication bias, such as grey literature and a wide range of hand-searched sources (Page et al., 2021a). No studies were included from these sources as they were either not retrievable or were only available in languages other than those included by the eligibility criteria. For this review, it could be speculated that – had the large number of Chinese trials of acupuncture and Chinese herbal medicine for AF been retrievable and/or translatable – the language and location biases discussed above may nonetheless have conferred a degree of (effectively) publication bias. It has been repeatedly demonstrated that trials conducted in developing nations, and/or published in languages other than English, show larger effect sizes and more positive results (Panagiotou, Contopoulos-Ioannidis and Ioannidis, 2013; Vickers et al., 1998).

Complementary therapy trials are also highly likely to be published in a language other than English (LOE) *irrespective* of the nature/direction of their results (Xia, Wright and Adams, 2008). The evidence base for many complementary therapies is strongly associated with the countries or regions where those therapies are indigenous and/or widely integrated into the healthcare system

(Lim et al., 2015). For example, in two of the therapies included in this review (yoga, acupuncture) a large proportion of the published global research effort is centred in the country of origin (India and China respectively) and published only in domestic journals in LOEs (Consentino et al., 2018; Field, 2016; Ma et al., 2016; More et al., 2016). This adds considerably to the difficulty of access for non-domestic researchers, inflating the risk of location bias in systematic reviews that include complementary therapies. Compounding this, the fact of publication only in domestic journals – which are not published in English and therefore not indexed by Euro-Western bibliographic databases – leads to a risk of language bias in systematic reviews of complementary therapies carried out by non-native reviewers. An AF-specific example of this is Wang et al.'s overview of systematic reviews on Chinese herbal medicine treatment for atrial fibrillation (2020), which searched three Euro-Western and four Chinese databases, finding a total of five systematic reviews in the former compared with 173 (in Chinese only) in the latter.

Access to journals published domestically, exclusively in domestic languages, is notoriously difficult for reviewers outside the country in question. This has been demonstrated with particular reference to Chinese databases: access is difficult as Chinese databases provide only limited access to viewers outside the Chinese mainland and territories (Adams et al., 2012; Xia, Wright and Adams, 2008). Even if access to these databases was straightforward, not all review teams have sufficient breadth of language skills to read and assess the retrieved papers (Jiao, Tsutani and Haga, 2013). This issue is particularly relevant to this review, which identified a high number of candidate studies that were marked for full-text review but could not be retrieved. On the basis of their titles and English-language abstracts (where available), these studies were likely to be relevant, and the fact of their exclusion must be regarded as a serious compromise of the validity of this review.

It has been demonstrated that language restrictions in systematic reviews do not change estimates of effectiveness in reviews of conventional medicine (Nussbaumer-Streit et al., 2020), but substantially change estimates of effectiveness in reviews of complementary therapies. In a landmark paper by Pham et al. (2005), the findings of 42 systematic reviews were subjected to sensitivity analyses showing the effects of both including and excluding papers not in English: one particularly stark example was the re-analysis of a systematic review of acupuncture for smoking cessation which included papers on seven English-language trials and five non-English-language trials (White, Rampes and Ernst, 2002); the analysis of all 12 papers demonstrated a non-statistically significant 21% (OR=0.79; 95%CI = 0.55–1.11) greater effectiveness of acupuncture for smoking cessation than sham controls. However, when re-analysed by Pham et al. to exclude non-English-language papers, the effect of acupuncture was just 7% (OR=0.93; 95%CI = 0.58–1.49); conversely, when re-analysed to include *only* non-English-language papers, the effect of acupuncture was substantially greater at 31% (OR = 0.69; 95% CI = 0.39–1.21). More recently, the work of Dechartres et al. (2018) demonstrated that, across 5,659 randomised controlled trials

included in 698 meta-analyses published between 2011 and 2017, treatment effects were larger for trials published in LOE (combined ROR = 0.86; 95%CI = 0.78–0.95).

3.6.2.i The "prove/improve" paradigm

Amplifying the risk of language/location bias, indigenous complementary therapy research programmes tend to follow a qualitatively different agenda. In countries of origin, the effectiveness of the therapy under investigation may be largely a given, and the overall direction of travel for research programmes therefore tends towards a nuanced approach to effectiveness in which different dosages or modes of a therapy are compared to identify the most effective (Scheid and MacPherson, 2012). Compare this with complementary therapy effectiveness research programmes in the West, which seek primarily to demonstrate either the equivalence of complementary therapies with a conventional standard of care, or the superiority of complementary therapies when used adjunctively with standard care (Flower, Scheid and Lewith, 2012; Hsu, 2012).

This qualitative difference is aptly summed up by Thomas and Fitter as the "prove/improve paradigm" (2001), and it may go some way to explain the difference in results from searches of indigenous compared with Euro-Western repositories. To illustrate: Wu et al. (2013) found that 115 of 119 trials of Chinese herbal medicine for coronary artery disease could only be found in three Chinese-language databases, compared with the five English equivalents yielding the remaining four trials. The disparity may be partly a consequence of the qualitative difference in approach. A Euro-Western 'prove' research agenda is less likely to field a seemingly wildcard intervention such as Chinese herbal medicine for a life-limiting illness such as coronary artery disease; this is more likely the territory of an 'improve' research agenda associated with an indigenous research programme published domestically in a language other than English, and therefore less likely to be indexed in Euro-Western bibliographic databases. Supporting the findings of Wu et al., this review identified 222 Chinese trials of acupuncture and Chinese herbal medicine for atrial fibrillation via Chinese databases, compared with one trial of acupuncture and three Chinese herbal medicine trials identified in Euro-Western databases. For complementary medicine review teams without access to these databases, or language skills to translate papers, the potential for bias is clear.

3.6.2.ii Quality of complementary therapy trials

Access is an issue, but quality is also an issue. Efforts to retrieve domestically published reports of complementary medicine research may not be rewarding because the quality, and reporting quality, of complementary therapy trials may not be optimal, especially when published in domestic journals. Adams et al. (2012) found that searching Chinese-language databases for trials of Chinese herbal medicine yielded substantially increased numbers of papers, but that methodological flaws in the papers led to their exclusion from reviews; Pan et al. (2017) found

similarly that in an analysis of 119 trials of Chinese herbal medicine for rheumatoid arthritis, all 119 were at high risk of bias. This review similarly found that two of its three non-English language studies were judged to have a "some concerns" risk of bias, and the third had a high risk of bias – all of which may have excluded them from statistical synthesis, had statistical synthesis been possible.

The methodological and reporting quality of trials inevitably feeds forward into the certainty of evidence provided by systematic reviews of complementary medicine. For example, Jin and colleagues studied the certainty of evidence in systematic reviews and meta-analyses of Chinese medicine interventions published in Chinese journals, downgrading confidence in the reviews' effect estimates across all dimensions of the Grading of Recommendations Assessment, Development and Evaluation tool (GRADE); the most frequent reason for downgrading was risk of bias in the included studies (Jin et al., 2016).

Poor reporting quality in trials may also affect methodological quality. In a bibliometric analysis of 81 Chinese trials of integrative medicine for colorectal cancer, Chen et al. (2018) found overall low standards of adherence to the CONSORT reporting guidelines, putting studies at "some concerns" risk of bias and validating similar findings in this review. In 2017, Dechartres and colleagues published an investigation of 20,920 trials (conventional and complementary medicine) extracted from 2001 reviews published in the 30 years to 2014, using the original review authors' judgements of unclear risk of bias as a proxy for poor reporting. A notable finding was that poor reporting was most frequent in reviews published in journals with lower impact factors; these findings are congruent with those of this review, whose included studies were mostly (n=9/N=10) published in journals with an average impact factor of 2.4±0.7.

To investigate the association between journal impact factor and the CONSORT reporting scores of this review's included studies, a Pearson's correlation was carried out. Both variables were normally distributed, as assessed by Shapiro-Wilk's test (p >.05); there was a strong positive correlation between the journal impact factor and the CONSORT reporting score (r = >.5). Although there is no good reason to assume a causal link, much research on complementary medicine is published in journals with low impact factors (Ng, 2021), suggesting the potential for poor reporting and therefore "some concerns" risk of bias.

3.6.3 Individualised complementary therapies for AF

This review set out to identify the effect of 18 complementary therapies in relation to AF symptoms and HRQoL. Despite an extensive search strategy intended to retrieve studies of "whole" therapies, the included studies uniformly adopted a standardised subset of the therapy in question – such as a pre-specified yoga programme, a single herbal remedy or nutritional supplement, or a fixed set of

acupoints. In short, there would appear to be no studies investigating the effects of complementary therapies for symptoms and HRQoL in atrial fibrillation that take a pragmatic approach, mirroring the real-world practice of any complementary therapy defined in this review. The difference between a standardised protocol and the real-world practice of individualised complementary therapies will be discussed in the next chapter, and the requirement for pragmatic trials investigating such therapies will be outlined and justified. For this review, the effect of these "protocolised" therapies is largely to limit generalisability to real-world contexts of the individual studies' findings, and by extension the findings of this review.

3.6.4 Safety in the included studies

This review cannot provide an overview of the safety of complementary therapies for atrial fibrillation; the number of included studies is too small, and the number of therapies represented too narrow to give any indicative outcome. However, it can be demonstrated that the safety of the included studies compares favourably with other investigations of safety in complementary therapies. Witt et al.'s 2009 investigation of acupuncture safety across 229,230 patients receiving an average 10.2 treatments found that 8.6% experienced at least one adverse event, of which 2.2% required further treatment. Similarly, a survey of 1,008 complementary therapy users in Norway found that just n=50 (5.0%) of respondents reported adverse effects of treatment across a range of 19 therapies, with adverse events being "minor and transient" (Kristoffersen et al., 2022). The safety profile of this review's studies improves on both these studies: just n=37 (3.9%) of 960 participants from eight studies experienced a harm of mild and self-limiting nature. However, two studies (both yoga) did not report on harms, and these figures must therefore be regarded as only a partial representation of the included studies' harms. Additionally, the protocols and isolated elements of the therapies investigated by the included studies mean that these safety findings are not generalisable to routine practice settings, where a wider range of clinical techniques and strategies are combined in each therapy.

3.6.5 Strengths, biases and limitations of this review

3.6.5.i Strengths

A strength of this review was its rigorously researched search strategy, covering a variety of source types including grey literature and non-English-language repositories; such a strategy may mitigate some of the language and location bias inherent in reviews of complementary therapies. Within this, extensive backward citation searching of analogous reviews not only located relevant studies that otherwise would not have been identified via Euro-Western bibliographic databases, but also gave a

helpful indication of the extent of the evidence base that could not be retrieved, thus informing the conclusions of this review.

Another strength was the reviewer's extensive clinical knowledge of atrial fibrillation, which led to the identification of several important modifiers of effect via the analysis of clinical heterogeneity in the included studies. These effect modifiers – operating in the dimensions of population, intervention, setting and outcome – are recommended for use as covariates in future systematic reviews of interventions, and in trials of interventions for AF.

A final strength of this review was the reviewer's working knowledge of a wide range of complementary therapies, leading to the identification of limitations in generalisability (of the studies, and of this review) to real-world contexts. This indicated the need for pragmatic investigations of the effect of complementary therapies for AF symptoms and HRQoL, whose findings may be generalised to routine practice settings.

3.6.5.ii Biases and limitations

The conduct of this review by a sole reviewer must be regarded as a potential source of bias. This may be particularly evident in the selection of studies: as a subject expert in the area of complementary therapies, the reviewer may have made unjustifiable decisions regarding the exclusions of studies on the basis of their relevance (Lefebvre et al., 2022a); a second reviewer who was not a subject expert would have mitigated this potential bias. Double data extraction was also infeasible, and may have led to some errors in data extraction (Mathes, Klaßen and Pieper, 2017; Buscemi et al., 2006) despite the iterative checking process.

A further aspect of this review at risk of bias as a result of a sole reviewer is the restriction of eligibility criteria to reports of studies published in just three European languages. As discussed above, for a review of complementary therapies – of which a large proportion are published in languages other than English – this represents a significant limitation. In particular, the inability to retrieve 222 records from Chinese databases, including a significant proportion of trials that – on the evidence of title and abstract – may have been relevant to this review, must be regarded as substantially weakening the validity of the review. Additional reviewers with Chinese language skills may have been able to translate papers for inclusion, resulting in a more comprehensive search yield and less bias in the outcomes (Walpole, 2019).

Another, related limitation of this review is that searches – having set out to identify "whole therapies" – did not include search strings to identify specific individual elements of any therapy (for instance, "herbal medicine" was sought, but "Wenxin Keli" was not). Therefore, unless the title or abstract (typically) of a given study mentioned the therapy (or synonyms) of which the element was

a part, this review may not have identified it. There is a possibility of the exclusion of potentially relevant studies and a consequent degree of bias (Wider and Boddy, 2009).

Finally, the inclusion of studies that investigate only a standardised protocol or a single element of a complementary therapy limits the generalisability of this review's findings to real-world contexts.

3.7 Recommendations for future research

To avoid perpetuating language and location biases, it is recommended that future systematic reviews should search a wide range of source types to mitigate publication, language and location biases. This should include elements in the search strategy that allow identification of specific individual components of complementary therapies, with iterative searching to include terms used in those records already retrieved. The strategy should also include backward citation searching on analogous reviews to identify relevant studies that may otherwise not be identified by Euro-Western bibliographic databases.

It is also recommended that future reviews of complementary therapies with a substantial domestic publishing base in a language other than English should include at least one review team member able to retrieve and translate records/studies from relevant domestic sources. If the databases are Chinese, this may entail the researcher being situated on the Chinese mainland to allow access to a full range of resources.

Future reviewers should also include multiple team members to avoid bias in the study selection and data extraction stages.

It is recommended that future triallists of interventions for AF collect and report data on the effect modifiers identified by this review in the dimensions of population, intervention, outcome and setting, specifically the presence and duration of comorbidities alongside duration of AF; and that these are used as covariates in prespecified analyses of effect. Similarly, future review teams should use these covariates in meta-analyses of the effects of interventions for AF.

A specific finding of this review is that there appear to be no pragmatic trials providing real-world evidence regarding the effect and safety of complementary therapies on symptoms and HRQoL in AF. The standardised subsets of the therapies included in this review do not represent real-world practice of the therapies; the studies and this review itself therefore share a low degree of generalisability to routine practice settings. There is a requirement for pragmatic investigations of complementary therapies for symptoms and HRQoL in AF.

3.7.1 Acupuncture and nutritional therapy for AF

Of the four therapies for which this review found some evidence, two were selected for investigation in a future trial in comparison with usual care (Zuidgeest et al., 2017b). Specifying two therapies in a single trial offers improved efficiency from a funding point of view (Hind et al., 2017), while also improving motivation to participate (Foster and Little, 2012).

The two selected therapies were acupuncture and nutritional therapy (NT). While there is some evidence for the effect of both therapies on symptoms in AF (see **Table 6** and **Appendix E**, item 8) neither therapy has been investigated for HRQoL in AF.

A further justification for the selection of these two therapies is their potential to address outcomes that are clinically meaningful to AF patients. The work of the International Committee on Health Outcome Measures (ICHOM) on standardised AF outcome measures has identified HRQoL and symptom severity as amongst the most important outcomes for patients that may be investigated using trial methodology (Seligman et al., 2020). In considering the typical therapeutic outcomes of the therapies included in this review (see **Appendix E**, item 1), other therapies target a more limited range compared with acupuncture and NT; these two therapies may therefore offer greater potential to address HRQoL and symptom severity (Langevin, 2021; Clarke et al., 2015; Jakes and Kirk, 2015).

Additionally, both therapies may be able to address a range of therapeutic targets, including the comorbidities of the typical AF patient, by means of a holistic, individualised approach. Holism in this context refers to a conceptualisation of health extending beyond the simple absence of disease to encompass body, psyche and spirit (World Health Organization, 1948); individualisation refers to each therapy's adaptation to the unique needs of the individual patient at a given point in time, and varying dynamically over time as patient needs vary (Nutritional Therapy Education Commission (NTEC), 2015; British Acupuncture Council, 2009). Both therapies achieve their outcomes by means of a combination of specific and non-specific effects, the latter term referring to wider components of treatment such as the focused attention and empathy of a consultation, the effect of sustained support and monitoring over time, the patient's treatment expectation, the patient-practitioner relationship, the patient's own characteristics, and any effects of these on the patient's sense of self-efficacy and ability to enact self-care (Bishop et al., 2021; Greco et al., 2016; Prady et al., 2015, 2013; Kaptchuk et al., 2008; Liu, 2007; Kaptchuk, 2002). In this way, "treating the patient and not the disease" (Birch, 2019a) can be seen as central to the approach of both therapies, a principle that resonates with the "look beyond the ECG, treat the patient" approach of conventional AF care (De With et al., 2019; Alings et al., 2013) and tallies well with the highly comorbid state of the average AF patient (Lip, 2023; LaMori et al., 2012).

Other factors justifying the choice of these two therapies as targets for investigation include their standards of professional practice, and availability to AF patients in the UK. Both therapies are widely available through a well-populated and accessible network of qualified practitioners (British Acupuncture Council, 2023; British Association for Nutrition and Lifestyle Medicine, 2023). Each is overseen by a professional body that is itself regulated by the UK Government's national governance network for complementary therapies (Professional Standards Authority, nd); each body defines and monitors scope of practice, together with standards of safety and professional conduct. Training is required to a minimum standard of undergraduate degree (British Acupuncture Accreditation Board (BAAB), 2020) or professional diploma (Nutritional Therapy Education Commission (NTEC), nd). As safety and level of professional training appear to be directly correlated (Chan et al., 2017; Witt et al., 2019), these features of both therapies' governance are highly relevant.

A final argument for the choice of these two therapies lies in the fact that each integrates self-care and lifestyle advice based on the individual patient's needs and therapeutic goals; this may be an important element of the effect of the therapies for AF patients, for whom lifestyle and behavioural change around modifiable risk factors has been shown to impact modifiable risk factors, improve HRQoL and/or reduce AF symptoms (AbuElkhair et al., 2023; Seo and Lee, 2023; Bittman et al., 2022; Nalliah, Sanders and Kalman, 2018; Gallagher et al., 2016). A small body of evidence shows that acupuncturists are able to effectively support patients to make self-care and lifestyle changes informed by Chinese philosophies of self-care (Pinto et al., 2022; MacPherson et al., 2017a), such as diet incorporating energetic principles informed by a patient's TCM diagnosis, or exercise using the principles of Tai Chi or Qi Gong (MacPherson et al., 2017a; Deadman, 2016). Nutritional therapy is similarly able to support patients with self-care/lifestyle change; practitioners are trained in behavioural support and lifestyle recommendations as central skills of the discipline (Nutritional Therapy Education Commission (NTEC), 2015), and a small body of evidence shows the positive effects of nutritional education of patients (Poddar et al., 2010; Francis, Taylor and Haldeman, 2009).

3.8 Conclusion

This review has answered the question "What is the evidence for the safety and effect of complementary therapies for symptoms and quality of life in atrial fibrillation?" with a narrative synthesis of 10 studies representing four complementary therapies (yoga, Chinese herbal medicine, acupuncture/acupressure and nutrition/supplementation). Studies were grouped by symptoms and quality of life, and synthesis was structured by therapy type and risk of bias; no studies were

excluded from the syntheses. In the Symptoms domain, 18 outcome measures (2,027 (92.3%) observations) favoured the intervention, one (60 (2.7%) observations) favoured the control and two (108 (4.9%) observations) showed no effect. In the Quality of life domain, 25 outcome measures (1,627 (88.3%) observations) favoured the intervention, two (146 (7.9%) observations) favoured the control and one (69 (3.7%) observations) showed no effect. Additionally, a descriptive synthesis of the included studies' safety was conducted, demonstrating that the safety reported by the included studies was comparable with other studies of complementary therapies' safety.

The included studies demonstrated a high degree of clinical and methodological heterogeneity, and were also uniformly at either high or "some concerns" risk of bias, due in part to poor reporting that could not be addressed due to lack of response from corresponding authors. Statistical synthesis was infeasible due to the included studies' clinical heterogeneity, and inadvisable due to their high risk of bias. Clinical heterogeneity also made it infeasible to grade the certainty of evidence by outcome domain.

Strengths of this review include the extensive search strategy that sought to mitigate the language and location biases to which complementary therapy reviews are subject; and the reviewer's clinical knowledge of both AF and complementary therapies, leading to the identification of a number of important effect modifiers that are recommended for use as covariates in future trials and reviews investigating AF therapeutics.

Limitations of this review include the bias conferred by a single reviewer; the restriction of included studies to those published in a limited range of European languages; and the absence from search strings of specific individual elements of any therapy that may have excluded some eligible studies.

The studies included in this review used standardised protocols or isolated elements of the complementary therapies in question that are not representative of real-world practice of these therapies. This limits the generalisability of both the individual studies and this review to real-world routine practice settings. It is recommended that future research is carried out using a more pragmatic design than the trials in this review, allowing the investigation of a full extent of complementary therapies' effects. This argument will be developed and justified in the following chapter.

4 Methodology

This chapter discusses and justifies the methodological approaches of this feasibility study as a pragmatic trial of two complex interventions. Current guidance on complex interventions is discussed, using acupuncture and NT as illustrative examples, and critically evaluating the choice of mixed methods and pragmatic trial design in this context. The role of feasibility studies in determining feasibility of complex interventions prior to a large-scale RCT is considered. Finally, the philosophical foundations of Santé-AF's various methodologies are summarised.

4.1 Investigating complex interventions in healthcare

This section will critically discuss the concept of a complex intervention in healthcare, tracing its history up to the latest iteration of the principal guidance on the subject, and will provide an interpretation of acupuncture and nutritional therapy (NT) as examples of individualised holistic therapies that may be considered "truly" complex interventions. The current guidance will be critically considered in relation to investigations of individualised holistic therapies, using examples from acupuncture and NT. A strategy for investigating individualised holistic therapies will be briefly set out that may prove "philosophically valid, practically feasible and [able to] produce nuanced findings" (Warren, Melendez-Torres and Bonell, 2022, p.1)

4.1.1 A brief history of the MRC/NIHR guidance on complex interventions

The concept of a complex intervention is well-established in healthcare (Plsek and Greenhalgh, 2001), largely due to the work of the Medical Research Council in introducing an early definition in its *Framework for development and evaluation of RCTs for complex interventions to improve health* (Medical Research Council, 2000). This defined a complex intervention as a package comprising several distinct but interacting components, often focused on behaviour, purposefully designed to address a given combination of patient and/or condition characteristics. The guidance was radical at the time in acknowledging that healthcare interventions may be composite in nature, and the goal of research was therefore (broadly) to discover the effectiveness of such composites ("what works?"). Two further iterations updated and extended the original Framework (Moore et al., 2014; Medical Research Council, 2008), and a raft of explicatory and supporting literature developed the theory and practice of investigating complex interventions (Evans et al., 2019; Braithwaite et al., 2018; Bleijenberg et al., 2018; Craig et al., 2018; Pfadenhauer et al., 2017). All three iterations became highly influential in healthcare research (Wareham, 2021; Craig and Petticrew, 2013).

The guidance was also the subject of critique, one theme of which focused on the linearity of its complexity model (Braithwaite et al., 2017; Cohn et al., 2013; Kernick, 2008). Linearity in this sense refers to the relationship between the input and output of a system: in a linear system the output is directly proportionate to, and predictable from, the input. Linearity may be equated with causality, based on the Newtonian principle that equal causes have equal effects, and therefore that effects co-vary with their causes (Gershenson and Heylighen, 2005). By contrast, complexity science holds that in a complex system, the relationship between input and output (or between cause and effect) is non-linear, disproportionate and often unpredictable: multiple positive and negative feedback loops, more heuristic than algorithmic, reverberate together to magnify or attenuate output, which becomes less determined than stochastic, "fuzzy" or even chaotic (Braithwaite et al., 2017; Richards, 2015; The Health Foundation, 2010; Gershenson and Heylighen, 2005). Although the early MRC guidance acknowledged "the length and complexity of causal chains linking intervention with outcome" and encouraged researchers to "[pick up] unintended consequences… where possible" (Medical Research Council, 2008, pp.7–8), its critics found an essentially simple, Newtonian concept of causality apparent throughout, despite remaining largely unarticulated (Greenhalgh and Papoutsi, 2018).

With a less abstract focus, other critics discussed the perceived failure of the guidance to provide a means of defining a complex intervention, as distinct from a simple one. Citing multiple intersecting influences of metabolism, allergies, gut motility, psychological motivation and patient beliefs, adherence, patient-doctor relationship, doctor preferences, and societal/community beliefs, Richards (2015) concluded: "All this, just for a short-term dose of an antibiotic… on close examination it would seem that there is barely any intervention that we should not consider as 'complex'" (p.2).

In 2021 a revised and expanded version of the original MRC guidance was published. This iteration, current at the time of writing, is a National Institute for Health Research (NIHR) Health Technology Assessment titled *Framework for the development and evaluation of complex interventions* (Skivington et al., 2021b) ("the (NIHR) Framework"). The NIHR Framework is explicitly informed by more sophisticated theories of complexity science than the earlier iterations; it defines complexity as occurring *within* the multiple components of an intervention or *between* the intervention and its context – for example, when the intervention's outcomes are influenced by factors such as the context of its implementation or the patient's characteristics. The guidance also widened the investigative focus from the simple *what works?* to a broader set of perspectives (efficacy, effectiveness, theory and systems: *what works, for whom, in what context?)* that support the inclusion of wider environments within the investigative frame (Skivington et al., 2021b).

4.1.2 Acupuncture and nutritional therapy as "truly" complex interventions

Santé-AF investigated the feasibility of two complementary medicine interventions. Acupuncture and nutritional therapy (NT) each have radically different antecedents and theoretical models (Bush et al., 2020; Scheid and MacPherson, 2012) but share a holistic conceptualisation of health that extends beyond the simple absence of disease (World Health Organization, 1948) to encompass ideas of health and vitality that integrate body, psyche and spirit, sometimes known as "whole systems" health (Mills et al., 2017; Deadman, 2016; Koithan et al., 2012). Holism understands the world as comprising interrelated and overlapping systemic entities with internal emergent self-organising structures, whose nature cannot be understood solely from an investigation of their constituent parts (Federoff and Gostin, 2009; Becht, 1974). In this sense, holism has an affinity with complexity science, and particularly with the features of complex adaptive systems. Both acupuncture and NT share core operational characteristics that embody the principles of complex adaptive systems:

- An iterative, holistic **consultation process**, taking account of the patient as a complex physical, mental and emotional "system" with a unique history, influenced by and adapting to wider complex systems including geopolitical, cultural, educational, social and financial; also interdependent with other dynamic dimensions such as personal lifestyle choices, health state and goals, and the therapeutic process itself;
- An element of **reflexivity** on the part of the practitioner that remains aware of the practitioner's own complex "system" – comprising the systems and dimensions described for the patient, above, together with professional skills, knowledge, preferences and attitudes – adapting this as required to modify its influence on the consultation/treatment process and on the patient themselves;
- The formulation, according to therapy-specific theoretical models, of an **intervention** that responds to the complex system of the patient, combining a number of interacting strategies pre-existing within the scope of the therapy;
- The **dynamic adaptation of the intervention**, often moment by moment during delivery, guided by the practitioner's own complex system, and taking account of observed and reported changes in the patient's complex system, and the interactions within and between all of these (Nutritional Therapy Education Commission (NTEC), 2015; British Acupuncture Council, 2009).

It is clear that both therapies conform to the definition of a complex intervention set out in the earlier iterations of the MRC guidance by combining a number of interacting elements within a single, or course of, treatment. Both also conform to the widened definition of complexity in the NIHR Framework by admitting complexity between those individual elements (intra-intervention) and

between the intervention and its wider context (inter-context). Neither requires efficacy testing, being established therapeutic modalities with real-world uptake, but the remaining three of the Framework's investigatory perspectives (effectiveness, theory and systems) are applicable.

It can also be seen that each therapy employs a model of complexity simultaneously broader, more granular and more dynamic than that premised by the NIHR Framework. *Broader*, in that the model extends inwards to include the complex systems of the patient and the practitioner, and outwards to include a wide conception of the overarching complex systems within which the patient and practitioner are nested, together with the interactions between all; *more granular* in that interventions are individualised at a low level, i.e., the individual treatment for the individual patient at the individual point in time; and *more dynamic* in that strategies are adapted to the changing needs of the patient at a low granular level, often during delivery. This broader, more granular, more dynamic complexity constitutes what could be called a "truly" complex intervention, and is a characteristic of many holistic therapies that base individualised therapeutic strategies on a systems model – including, for instance, physiotherapy, bodywork, herbal medicines, Ayurveda, and homeopathy (Stockley, 2022; Kimmel, Irran and Luger, 2015; Niemeyer, Bell and Koithan, 2013; Rioux, 2012; Bellavite, 2003). Fang and Casadevall feel the term "holistic" has "acquired a bad name, perhaps due to… new age pseudoscience" (p.1401), but when contextualised as above the term is both etymologically accurate and ontologically representative.

From this, it can be seen that individualised holistic therapies' model of complexity is web-like: change at one node interacts with change at other nodes, in a structure that Kaptchuk calls *synthetic* (i.e., organised by synthesis rather than linearity or causality). "The question of cause and effect is always secondary to the overall pattern. One does not ask, "What X is causing Y?" but rather, "What is the relationship between X and Y?" (Kaptchuk, 2000, p.4). It can also be understood that individualised holistic therapies' concept of complexity, as an essentially fractal patterning, is repeating and self-similar across temporal, spatial and categorical dimensions; thus, in a holistic therapeutic model, the complex adaptive system of the patient stands in some kind of ontological relationship with a possibly infinite number of complex adaptive systems both internal and external to their own. By contrast, biomedicine, as Kaptchuk remarks, is "primarily concerned with isolable disease categories or agents of disease, which it zeroes in on, isolates, and tries to change, control, or destroy. An ontologically circumscribed entity is the privileged ideal of the system" (p.3).

4.1.3 Investigating individualised holistic therapies with the NIHR Framework

Holism is often placed in opposition to the reductionism that originally emerged from the Cartesian separation of body, mind and spirit (Valles, 2020; Schaffner, 1981) and which now underpins both

conventional biomedicine and much of the scientific method used to investigate it (Ghaemi, 2015; Greenhalgh, 2012; Krieger, 2011; Kubsch et al., 2007; Foucault, 1973). Briefly, reductionism holds that all entities are made up of constituent elements, and insight into the entities may be gathered from an examination focused at the level of those constituent elements (Verschuren, 2001). In biomedical healthcare, reductionism conceives the patient as a largely biomechanical entity in which the constituent parts may be discretised, investigated, and – in a healthcare sense – treated (Marcum, 2004; Beinfield and Korngold, 1991; Carlson, 1979).

It is clear that the complexity models of both biomedicine and individualised holistic therapies are artefacts of the more reductionist or more holistic paradigm on which each is respectively founded. It is also clear that individualised holistic therapies' complexity model extends beyond the "ontologically circumscribed" equivalent of the NIHR Framework, which admits complexity only between the components of the intervention itself and/or between the intervention and its context. In the NIHR Framework, it is an important point that while *context* may extend beyond the strict confines of healthcare (Pfadenhauer et al., 2017), the Framework is unequivocal that when investigating a complex intervention it is impractical to follow principles of extensibility beyond a point. "To make an evaluation tractable," the authors write, "it will be necessary to limit its scope by determining a system boundary and restricting the range of potential mechanisms or explanations that are investigated" (Skivington et al., 2021b, p.23). In other words, to investigate complexity, complexity must be simplified.

This conscious and explicit boundary-setting is paradigmatically indicative; as Cohn et al. remark: "the 'ecological' character [of complexity]… inherently challenges the conventional standards of reproducibility and fidelity that govern the development and testing of health interventions" (Cohn et al., 2013, p.40). Earlier iterations of the complex interventions guidance sat comfortably within the reductionist paradigm because they implicitly excluded levels of complexity that could jeopardise those fixed ontological points represented by the epistemology of reductionist investigatory methods – in particular, the randomised controlled trial's representation of causality, and its allied concept of generalisability (Deaton, 2020; Valles, 2020; Hamwee, 2019; Hariton and Locascio, 2018). But in relation to systems-level complexity (and certainly in relation to a "truly" complex intervention) this proxying produces unreliable results: wherever complex systems interact, individuality accrues, generalisability is diminished, and causality becomes less clearly attributable. For investigators to be able to apply the standard hypothetico-deductive approach, it is necessary to put some boundaries around the investigation.

But when complexity is re-complexified – as the 2021 Framework also begins to do – the tensions between reductionist investigative methods and systems-level dynamic unpredictability are less easily elided. On the one hand, the Framework declares itself to be informed by complexity theory

and systems thinking, and widens complex interventions' investigative focus to enfranchise four different perspectives (efficacy, effectiveness, theory and systems); there is also an effort to de-platform the RCT, or at any rate to have alternative methodologies join the RCT on the platform: "extensions to standard… randomised controlled trials (including adaptive designs, SMART trials… n-of-1 trials, and hybrid effectiveness-implementation designs)… non-randomised designs and modelling approaches… natural experiments or systems evaluations" (Skivington et al., 2021a, p.7). On the other hand, the extent of complexity that can be investigated is still rigorously restricted (only intra-intervention and inter-context), and investigators are explicitly prohibited from extending the field of investigation, in direct contradiction to the fractally extensible nature of complexity. These contradictions inevitably point the Framework back to reductionist philosophical foundations despite its own best efforts to engage with complexity.

The incompatibilities between reductionist and holistic paradigms, held in close tension in the NIHR Framework, are reflected in what could be termed *operational* incompatibilities between the Framework and a "truly" complex intervention in the shape of an individualised holistic therapy. This incompatibility can be illustrated using examples from acupuncture and nutritional therapy; there are differences between the investigative processes outlined in the NIHR Framework and the therapies' general modus operandi that may have implications for research into their effectiveness, theory and systems perspectives.

One important difference focuses on adaptivity (of the intervention) in the context of the patient. Reductionist method, as in the NIHR Framework, envisages an intervention to target the collective (pathological) characteristics of a *group:* what has been described as "the selection of homogeneous samples described in enough detail for meaningful comparisons to be made across studies" (Paul, 1967). This core principle of scientific method automatically positions the patient at a higher level of granularity, pointing up the difference of therapeutic proposition between the range of an individualised holistic therapy available to the patient at every appointment, and the single, targeted, pre-designed intervention envisaged by the NIHR Framework. Where the latter can permit a degree of adaptivity only so far as it keeps the intervention congruent with the target characteristics of the patient *group*, the former is equipped to work adaptively with every *individual patient*, with or without a core symptomatology. It is axiomatic in Chinese medicine, for instance, that six different patients visiting a GP with certain symptoms will all receive the same diagnosis and the same or similar medications; but the same six patients visiting an acupuncturist will most likely each get a different Chinese medical diagnosis, a correspondingly different set of treatment principles and a different points prescription (Kaptchuk, 2000). This is because the exact cluster of *patterns of disharmony* (a lower level of granularity than the disease classifications of biomedicine) arise out of the patient's uniqueness: one biomedically-defined disease might translate to a hundred

Chinese clusters of patterns of disharmony, if the same symptoms were observed in a hundred different individuals (Scheid, 2002). The individualised treatment responds to that unique cluster.

In investigatory terms, it is easy to see how this differs from the conception of the patient as implied by the NIHR Framework. While the Framework's patient is acknowledged as being subject to varying influences including geographical, epidemiological, sociocultural, socioeconomic, ethical, legal, political (Pfadenhauer et al., 2017), investigations are premised on, and results extrapolated to, a group level defined by a necessarily limited number of common characteristics that constitute a level of homogeneity congruent with population generalisability. This issue is familiar in the field of multimorbidity research, where the requirement of reductionist investigative principles to limit the number of variables in the investigation has led to a dearth of research into safe, effective treatments for patients with multiple comorbidities (Loring et al., 2020; Academy of Medical Sciences, 2018; Caughey and Roughead, 2011).

As conceived by the NIHR Framework, the intervention itself must also have a predefined adaptivity. In fact, the intervention is relatively static in that it is designed in advance of delivery; so too is a defined extent of *refinements* (fine-tunings) and *adaptations:* "Adaptation [is] where an existing intervention is modified or tailored to adapt it to a new population, setting or context" (Skivington et al., 2021b, p.xxi). The effect of this is to make the entire intervention development, testing and evaluation cycle distinctly undynamic: the thinking is done in advance, and changed in a process that takes account of the population, setting or context in question, rather than the individual patient at hand. By contrast, an essential part of individualised holistic therapies' approach is derived from adapting interventions dynamically, at the low level of granularity represented by the individual patient. Indeed, because an individualised holistic therapy seeks to *treat the patient, not the disease*, a given treatment may address a wider range of disease symptoms, or sometimes symptoms altogether different, than those targeted by a focused, pre-designed intervention for a single health condition (Birch, 2019b).

These sometimes radical adaptations are part of everyday routine practice in individualised holistic therapies, but in terms of the general shape of interventions (and investigations into them) that are envisaged by the NIHR Framework, they may be troublesome. One example of this is the patient who does not receive the intended intervention: for instance, many practitioners have had the experience of seeing a patient who simply talks for the duration of the appointment without receiving the intended therapy, but who departs declaring themselves to feel "so much better". From the practitioner's point of view, if the goal is to *treat the patient, not the disease* then a treatment consisting wholly of talking would certainly qualify as an effective therapeutic encounter. But if a complex intervention is pre-designed to include the therapy, then a treatment so fully adapted to the specific needs of that patient at that point in time as to omit the therapy entirely,

would be difficult to describe as a therapeutic encounter – and certainly difficult to either replicate or generalise. By designing a somewhat complex intervention with a pre-specified extent of adaptivity for a genericised patient, the NIHR Framework preserves the parameters within which causality may be attributed, along with a degree of generalisability in terms of population. But for an individualised holistic therapy, in which many aspects of the intervention may contribute to change, and many aspects of the context may complexify the intervention (Fei et al., 2022), generalisability might be considered not only philosophically, but also practically, untenable (Evans et al., 2019; Cambon et al., 2012).

A final point of difference is the absence of the practitioner as an agent of change beyond the delivery of the intervention. The NIHR Framework does not consider practitioners as complex adaptive systems in their own right: as discussed, complexity as defined by the Framework occurs only between intervention components or between intervention and context. Of course, the practitioner may be subsumed under the heading of 'context'; every iteration of the MRC/NIHR guidance has specified a goal of complex interventions research to be an understanding of "how an intervention works and how this may vary across different contexts or for different individuals" (Skivington et al., 2021b, p.22), to which the investigator of complex holistic therapies might add "when delivered by different practitioners". A well-established mitigating principle is to include the practitioner as covariate in analyses (Wester, Rubel and Mayer, 2022; Paul, 1967), but if the practitioner is to be considered a complex adaptive system, a potentially unmanageable number of covariates must subsumed under the "practitioner" entity. By eliding practitioner and patient as complex adaptive systems, the Framework renders both as transparent entities delivering or responding to the intervention in more or less algorithmic ways – but in a truly complex environment, they, and their respective effects, are not so determinable.

4.1.3.i Reconciliatory strategies

Is it possible for an investigation using essentially reductionist methods to produce a full representation of individualised holistic therapies? Some possible approaches may be found in other sciences, where models of reconciliation between holism and reductionism are instructive. For instance, in the world of genomics, Delker and Mann (2017) note that the derivation of phenotype (an individual's characteristics resulting from genetic expression) from genotype (the individual's genetic constitution) requires a detailed understanding of both entities, together with an understanding of the interactions that occur in space, time and different developmental levels of the systems; all dimensions, they argue, are needed to produce a full understanding. This model could be analogised to the micro, meso and macro models of perspective that originated in evolutionary economics (Dopfer, Foster and Potts, 2004) and are now employed across social sciences, health and management sciences; here again, the authors suggest that an understanding of each level,

and the interactions between them, is required to comprehend the whole. Similarly, ecology – a branch of science in which complex adaptive systems form the core unit of study, which has long required transcendence of a reductionist paradigm – has proposed a model known as "restricted complexity", based on an understanding of process at all levels of a complex system and derived from the understanding of laws governing complexity rather than complexity itself (Riva et al., 2023). The principles are "complementary *and* antagonistic", as articulated by the French philosopher Edgar Morin in a seminal 1992 paper:

> System theory thought it had overcome… the atomization of reductionism; on the contrary, however, its "holism" becomes a new kind of reductionism by reducing everything to the whole (Morin, 1992)

Appropriately enough, Morin's "complementary *and* antagonistic" conception owes something to the metaphor of yin-yang, the constant dynamic transformation-of-opposites process central to classical Chinese thought and a foundational principle of Chinese medicine. Developing the theme, Fang and Casadevall (2011) argue that reductionism and holism are not true opposites, and that the inherent weaknesses of each produce occlusions that can only be supplied by the other: "a combination of reductionistic and holistic approaches can be synergistic… are in fact interdependent and complementary," they write (p.1403). More plainly put: in its data-richness, holism may not adequately represent the linear causalities that reductionism excels in detecting; conversely, reductionism's point-specificity may exclude relationships within and between systems, needing the perspectives of holism to understand relational influences. Arguing for better means of evaluating complex interventions, Paparini et al. set out a compromise: "The conventional scientific quest for certainty, predictability and linear causality… has to be augmented by the study of uncertainty, unpredictability and emergent causality in complex systems" (Paparini et al., 2020, p.5).

In research terms, Paparini et al.'s *augmentation* suggests a reconciliatory approach, and perhaps the auspices of pragmatism to foster that reconciliation. Pragmatically, no matter how complex and/or holistic the intervention under investigation, it is necessary to introduce some restrictions in scope – if only to avoid ending up in a "wicked problem" scenario in which poorly-defined and therefore mobile investigative parameters render the question unanswerable (Rivett, 2012). The holistic paradigm's extensibility is logically infinite; even if research methods were sufficiently elastic, the limits of human vision (physical, intellectual, metaphorical) cannot possibly comprehend the fractal infinity of complexity. "Looking at something as a whole is a fiction… the observer necessarily focuses on one or some aspects or particles of an object at a time," Verschuren observes (2001, p.393). To some extent, then, in service of Skivington et al.'s injunction to tractability, a short-term dose of antibiotics remains just that – a short-term dose of antibiotics.

There is an obvious parallel here with the daily practice of individualised holistic therapies. While practitioners strive to see the whole patient as comprised of, and interactive with, multiple internal and external complex adaptive systems including the practitioner's own, they are inevitably constrained in both apprehending and responding to that complexity by a host of quotidian parameters such as appointment duration, professional fees, and the nature and extent of their own skills. Some part of the practitioner's skill lies in judging what treatment can be delivered within those parameters; choices must be made, or the patient goes untreated. This same pragmatism is evident where practitioners make a choice – at individual patient level, at programme level, sometimes at qualification or training level – to forego the full extent of individualisation and instead focus on a standardised treatment protocol. This is particularly the case in specialisms such as fertility (Paulus and El-Danasouri, 2002), pain (Crowell et al., 2020), and addiction (Stuyt, Voyles and Bursac, 2018).

Therefore, in investigatory terms, we are brought full-circle back to the NIHR Framework's advocacy of boundaries: an ontologically circumscribed entity must be substituted for the whole, in order to apply investigatory principles.

4.1.3.ii Research approaches for individualised holistic therapies

The debate of the two-plus decades since publication of the first MRC guidance has led to a creative blending or repurposing of methodological approaches that may be able to reconcile, to varying degrees, the principles of reductionism and holism, thereby providing some possibilities for accommodating research into individualised holistic therapies as "truly" complex interventions. Mooted approaches include "whole systems research" (Langevin et al., 2011; Paterson et al., 2009; Verhoef et al., 2005); the use of logic models for modelling complex interventions (Mills et al., 2017); the incorporation of narrative and phenomenological approaches (Valles, 2020; Hsu, 2012; Charon, 2008; Marcum, 2004); the repurposing of the complexity-based static and dynamic analytic models used in epigenetics to evaluate many variables simultaneously (Ahn et al., 2010). Often in complementary medicine research, the intervention itself – rather than the methodology – bears the burden of creative adaptation, self-inflicting its own ontological circumscriptions as in the pragmatic simplification of "semi-protocolization" (Fei et al., 2022; Stringer et al., 2022; Conboy et al., 2016), or indeed the protocolisations or single elements of therapies investigated by the studies included in **Chapter 3**.

Another methodological approach is represented by so-called "realism", a repurposing from social science that aims to develop theory regarding *what works, for whom, in what circumstances, and how* (Jack, 2022; Palm and Hochmuth, 2020); such theory is said to allow a more reliable representation of generalisability. Despite being introduced to healthcare almost a decade ago (Fletcher et al., 2016; Jamal et al., 2015), only a few healthcare examples of realism currently exist,

although it is increasingly common to find a realist process evaluation nested within a (usually pragmatic) trial (Renmans and Castellano Pleguezuelo, 2023) (a structure sometimes known as a "realist RCT"). Realist methods have been criticised as incompatible with the postpositivist paradigms of the RCT (Van Belle et al., 2016), but the methodology has been defended as "philosophically coherent, practically feasible and can produce nuanced findings" (Warren, Melendez-Torres and Bonell, 2022) (a description that could be regarded as a holy grail of investigative techniques for research into truly complex interventions).

The NIHR Framework itself lists a number of methods based on a trials model, including Sequential Multiple Assignment Randomised Trials (SMARTs), stepped-wedge and adaptive designs (Ajmera et al., 2021; Pallmann et al., 2018; Copas et al., 2015; Almirall et al., 2014). Such designs incorporate a degree of methodological adaptivity that allows for interventional adaptations – typically a pause in analysis and adjustment of the intervention within pre-specified parameters. Such designs aim to adapt the intervention to the population and context, emerging with a version of the intervention that works for as much of the population in as many contexts as possible; but since individualised holistic therapies have already arrived at this version of themselves in daily practice, these designs may be thought somewhat inapplicable unless a protocolised version, as described above, is used.

The n-of-1 trials methodology, also cited by Skivington et al. as a possible methodology for the investigation of complex interventions, is a variation on a traditional crossover RCT in which the independent variable is manipulated for one or a small number of participants (i.e., participant(s) receive one or more interventions over time) in a concealed, randomised sequence interspersed with washout periods allowing the participant to function as their own control (Margolis and Giuliano, 2019); this is somewhat similar to the non-randomised pre-post studies included in **Chapter 3**. Advocates of n-of-1 trials suggest that they add rigour over the individual case study methodology, mitigating biases such as placebo effects, obsequiousness bias, treatment expectations and regression to the mean (Guyatt et al., 1988, 1986); but these benefits are partly conferred by blinding, and while this is possible for some types of individualised holistic therapies (naturopathy, herbal medicines) (Bradbury, Avila and Grace, 2020), blinding is not possible with therapies that have some participant-focused behavioural element. An interesting variation is the n-of-1 trial with purely biomarker outcomes, proposed in protocol form for nutritional interventions by Tian et al. (2020); the use of objective outcomes obviates some cognitive measurement biases, but by the same token disallows psychosocially-oriented outcomes, including those affected by treatment expectation, which may arguably be considered integral to some individualised holistic therapies.

Other, non-RCT approaches suggested in the Framework may also prove useful in evaluating individualised holistic therapies. These include network analysis, an observational, data-driven

method that may be able to detect changing relationships within a complex system (Hevey, 2018); qualitative comparative analysis, a mixed methods approach to establishing causality (Hill, Cooper and Parker, 2019); and modelling – not an investigatory approach as such, but a means of predicting intervention effects in wider contexts from known parameters using techniques such as fuzzy logic (Zhu et al., 2022).

Interestingly, pragmatism as a philosophy (or even in an applied form in the shape of the pragmatic trial) is largely absent from the Framework, although there are multiple instances of pragmatic trials in its 27 illustrative case studies. The absence may exist because pragmatism was considered more paradigm than definable methodology, or perhaps because it applies more to effectiveness than to efficacy perspectives. It is certainly the case that a pragmatic trial design – particularly if pragmatic in the dimensions of intervention scope and delivery – offers scope to investigate the effectiveness of an individualised holistic therapy in everyday practice (Groenwold and Dekkers, 2017; Knottnerus and Tugwell, 2017; Patsopoulos, 2011; MacPherson, 2004), and growing numbers of trials of individualised holistic therapies take this approach (O'Shea et al., 2022; Skolasky et al., 2020; Brinkhaus et al., 2019; MacPherson et al., 2015, 2013).

The Framework is explicit in encouraging a pluralist approach, advocating combinations of methodologies in composite studies with multiple research questions to focus on the varying aspects of a complex intervention interacting with its context. Minary et al.'s review of methodological pluralism in healthcare research (2019) has identified, to date, three common approaches to combining methodologies: adaptations to individual RCTs, such as pragmatic trials or cluster randomised trials; process or mechanism analysis nested within RCTs; and alternative methods to RCTs, such as realist evaluations and quasi/non-experimental designs. The authors concluded that no ideal method could be proposed to evaluate complex interventions, but their review demonstrated that, in practice, a combination of methods is often deployed to address linked questions of effect, implementation, mechanism and context.

The methodologically pluralist approach is reminiscent of the original MRC complex interventions guidance, and may pose similar problems: multiple methodologies compiled together may be no more capable of fully representing or investigating the effect of a truly complex intervention, than the original guidance's multiple-component conception of a complex intervention was itself a true representation of complexity. In the case of both investigated intervention and methodology, it is necessary to pay attention to the actions and interactions within and without the complex system to produce robust representations of complexity.

4.1.3.iii "Somewhere between systematic theory and absolute uniqueness": case study as investigational methodology

One form of methodology noticeably absent from the NIHR Framework – except, rather ironically, in the shape of its 27 illustrative examples of complex intervention investigation in action – is the case study. Despite long being regarded as one of the lowest tiers on most versions of the evidence hierarchy (Burns, Rohrich and Chung, 2011), the case study is enjoying something of a renaissance in healthcare research; the various work of Paparini, Papoutsi and Greenhalgh has been influential in rehabilitating the methodology as a means of both investigating, and representing the individually meaningful effects of, a complex intervention (Paparini et al., 2021, 2020; Greenhalgh and Papoutsi, 2018). In social science, the authors argue, case study methodology has been used to hypothesise causal inferences regarding the ways in which complex interventions achieve their effects, while considering the relationship between intervention and context (which, in a single-case report, has the potential to be as granular and idiosyncratic as ontological fidelity requires). Studying healthcare services, Anderson and colleagues (2005) suggested that the case study can facilitate the recognition and greater understanding of interdependencies, non-linearities, unexpected events, patterns and changing patterns within a complex adaptive system; in relation to clinical practice, case study methodology may afford these same understandings of complex patients, interventions, and contexts (including practitioners).

Paparini et al. (2021) have put forward a number of variations on the case study theme suitable for investigating complex interventions, including case series; case studies nested within RCTs or quasi-experimental designs; and longitudinal or cross-case analysis. Nesting case studies/case series within a pragmatic RCT would seem to offer possibilities for investigating "truly" complex interventions, combining the strengths of scientific method with the strengths of holistic method.

This proposition can be illustrated with reference to one particular individualised holistic therapy. Chinese medicine (the overall modality of which acupuncture is a part) is no stranger to the tussles between its own structural complexity and a reductionist paradigm; as a system of therapeutics constantly migrating between ancient East and modern West, and enriched by the localisations of each, reconciliatory strategies of representation have long been necessary at both theoretical and operational levels (Flower, Scheid and Lewith, 2012; Ward, 2012; Scheid, 2002). One such strategy, employed in the classic texts of Chinese medicine since the Han dynasty of the early first millennium, is recognisable in the modern West as a variation on case study methodology by means of which Chinese masters transmit knowledge to students. These "case reports", often in the form of a gnomic sketch, allow full play of the multidimensional idiosyncrasies of the patient, showing how these are met by similar idiosyncrasies of practitioner, treatment and context (not to mention the interpretational capacities of the modern-day reader). In this way, case study methodology becomes "a literate medium… somewhere between systematic theory and absolute uniqueness"

(Kaptchuk, 1997, p.xvii), a positioning that recalls Fang and Casadevall's perception of reductionism and holism as "synergistic… interdependent and complementary" (2011, p.1403).

Relating the practice of acupuncture explicitly to complexity theory, Citkovitz and Conboy suggest an even more radical possibility:

> "In health research, complexity science involves… collecting data from across physical body systems and wider biopsychosocial systems… designing complex interventions composed of multiple interlocking modalities that take all the data into account… measuring emergent and qualitative outcomes, and… responding to feedback loops that allow adaptation, over and over again, of the intervention to the participant. Acupuncturists just call that *Thursday afternoon in clinic*." (Citkovitz and Conboy, 2022, pp.24–36)

Of course, the authors' point is that acupuncturists were working at the intersections of context and complex adaptive systems long before the modern world found it necessary to invent the terms. But this wry reflection raises the interesting question of whether research into the effects of acupuncture – or any individualised holistic therapy – may be considered a real-world process, indivisible from practice. By Citkovitz and Conboy's reading, every practitioner is a developer and researcher of complex interventions, undertaking multiple investigations every day by tailoring multifactorial treatments to the needs of each individual patient, administering the treatment and testing its effects, recording emergent changes, and adapting the intervention to respond to change across multiple systemic elements; and all the while taking account of the interactions between the multiple complex adaptive systems both in the consulting room and in the wider world. Here, the practitioner's case notes may be considered analogous to, or at any rate the basis of, the case report. The output of pragmatic research – real-world evidence – is exemplified (Zuidgeest et al., 2017a), and traces of a theoretical-level pragmatism begin to appear, in the sense that research and routine practice settings are identical (Zwarenstein, 2017).

4.1.3.iv The pragmatic trial with nested case studies

In a methodologically pluralist spirit, pragmatic approaches to trial methodology incorporating some forms of nested case study methods may offer the possibility of integrating reductionism and holism at a philosophical level, while doing justice to the complexity of intervention, patient, practitioner and context (Paparini et al., 2021, 2020). This extension to a traditional pragmatic trial might offer a serviceable means of combining the strengths of reductionist method (preserving external validities via a narrow focus and well-defined variables) with the strengths of holistic method (a detailed representation of a range of intervention effects for a number of highly individual patients in their specific contexts with their specific practitioners). In this way, such an approach may be considered capable of producing evidence that is both reductionist and holistic. In complementary medicine, this hybrid methodology could also produce findings that are informative for practitioners

(Hutchinson et al., 2022), which may contribute to the use of research-based evidence in complementary practice (Armour et al., 2021); additionally, it may enfranchise practitioners in research efforts, supporting the development of robust research skills amongst practitioners of complementary medicine and raising the methodological quality of complementary medicine research (Veziari, Kumar and Leach, 2022, 2021).

Within this structure, findings at individual level may be suggestive for future research, may nuance the findings of a trial, and may facilitate effective deployment of interventions in other contexts (Ankeny, 2017) in a limited form of process evaluation; in turn, group-level findings may refract with individual findings to produce fuller understandings of effects, and may allow the adjustment of interventions during future delivery to respond to clusters of patient characteristics, or patient-context characteristics (Hesse-Biber, 2012).

Investigations of complex interventions in healthcare increasingly nest qualitative studies within trials, or conduct trials using mixed methods, but there are no known examples of nested case study methodologies (Minary et al., 2019). The growing interest in patient-oriented research (POR) and patient and public involvement (PPI) in trials may support wider use of this approach in future (Allemang, Sitter and Dimitropoulos, 2022).

4.2 Complex interventions, pragmatism and mixed methods

In investigational research, the strong affinities between pragmatism and mixed methods are amplified when investigating the effectiveness of complex interventions. The kinds of questions that drive much complex intervention research (what works, for whom, in what context?) imply a pluralistic approach that combines quantitative and qualitative paradigms under the umbrella of pragmatism. This section will outline and justify that pluralism, and its interconnections, in Santé-AF.

4.2.1 Pragmatic trials for complex interventions

For all that the MRC/NIHR guidance on complex interventions does not name pragmatic trials as a specific methodology, the guidance is embedded in a pragmatic spirit (Donald, 2018). Pragmatic trials – as originally defined by French statisticians Schwartz and Lellouch in 1967 (republished in 2009) – are a means of obtaining information that supports clinicians and patients to choose between alternative treatments as delivered in the real world (effectiveness). Although pragmatism is a spectrum, the fully pragmatic trial is defined in opposition to the fully explanatory trial. In the latter, a highly controlled investigatory environment is maintained to investigate the efficacy of a treatment with a minimum of confounding factors; by contrast, in a pragmatic trial treatments are

carried out in a variety of settings representative of real-world settings in which treatment would normally be delivered, thereby maximising generalisability of the intervention to a wider real-world context (Burchett, Umoquit and Dobrow, 2011). Patients are representative of a wide population with the healthcare condition of interest, and their real-world divagations from treatment are scoped into the investigation; crossovers to and from treatment are permitted, and controls are usual care rather than the placebo common in explanatory trials (Lai et al., 2017). Data collection in a pragmatic trial is ideally limited to the data collected in routine practice as part of the intervention or other existing assessments, and outcomes are those important to patients (Meinecke et al., 2017; Rengerink et al., 2017; Welsing et al., 2017; Worsley et al., 2017; Zuidgeest et al., 2017b, 2017a).

Perhaps the most important feature of the pragmatic trial that lends itself to the investigation of complex interventions is the absence of any attempt to investigate one or more components of an intervention in isolation (Giraudeau et al., 2022; Dal-Ré, Janiaud and Ioannidis, 2018; Verhoef et al., 2005). This gives pragmatism an immediate affinity with complex intervention investigations: the intervention is acknowledged as composite and the focus of investigation is the effect of the "package" rather than individual elements (Zwarenstein, 2017).

Complementary medicine in particular has strong reasons to embrace pragmatism, most clearly identified in the controversial use of placebo controls. A placebo requires firstly the effective isolation of an intervention's elements thought to be responsible for specific effects, and secondly the use of a sham version of that element indistinguishable from the verum equivalent (Howick, 2017; Kaptchuk et al., 2008). Some complementary therapies may have isolable specific effects and be "shammable", such as herbal medicine administered without an accompanying consultation; but for many complementary therapies it is not possible to understand which element of the intervention is responsible for specific effects (Paterson and Dieppe, 2005), and isolation is therefore not tenable. Equally, it is untenable to produce a "sham" version of a therapy whose effects rely entirely on self-enacted behavioural strategies, such as nutritional therapy or yoga. There may be an attempt to isolate a specific element – as in the example of sham versions of acupuncture – but the non-inert nature of many sham controls has been amply demonstrated to obscure the true effect of the verum therapy (Vickers et al., 2018; Benedetti and Dogue, 2015; MacPherson et al., 2014). As a result of these methodological issues, trials of complementary therapies have moved towards pragmatic methodologies, and away from placebo controls in favour of usual care comparators (MacPherson and Charlesworth, 2020; Zhang et al., 2015).

4.2.1.i Pragmatic trials and process evaluation

Process evaluations (PEs) are carried out to understand the implementation of a complex intervention, its mechanism of action, and how its context affects implementation and outcomes (Moore et al., 2014).

PEs may be particularly useful in addressing a common critique of pragmatic trials: that pragmatic trial findings, despite being focused on external validity (variously referred to in the literature as generalisability, applicability or transferability (Burchett, Umoquit and Dobrow, 2011)), may nonetheless be quite specific to the particular PICO investigated (Pawson, 2019; Thabane et al., 2015; Treweek and Zwarenstein, 2009). This may lead to problems and/or delays in implementing trial findings in real-world contexts that differ from those of the trial – what Haff and Choudhry call "know-do gaps" (2018).

A consideration of implementation is beyond the remit of this thesis, but it can be pointed out that some aspects of future trial feasibility investigated by this study may overlap with those of implementation in a real-world context, and therefore to an extent this feasibility study functions as a limited form of process evaluation. This is particularly evident in the use of mixed methods to consider questions of adherence (participants and practitioners), details of actual interventions delivered, practitioners' attitudes to the scope of practice, and participants' experience of the interventions.

A PE, and its associated logic model that represents the mechanisms of action of a complex intervention, may be more beneficial to the type of "bespoke-designed" complex interventions envisaged by the MRC/NIHR guidance (Skivington et al., 2021b) – i.e., not the established therapies investigated by this feasibility study. Nonetheless, a future trial may wish to investigate contextual issues via a PE embedded within the trial, such as fidelity of the intervention delivery, together with specific details of treatments, that may aid understanding of whether and how the interventions work in a variety of contexts – for instance, in patients with specific multimorbidity clusters, including those comorbidities identified in **Chapter 3** as important modifiers of effect; or for different combinations of treatment elements influenced by practitioner preference and skills (Jeong et al., 2020; Liu et al., 2019); or a combination of all these factors.

Moore et al. (2014) suggest that initial analysis of PE data may be positioned before analysis of any outcomes, which may help mitigate any bias, and may usefully detect reasons for heterogeneity (or homogeneity) in outcomes. Given the nature of a future trial as pragmatic, with various parameters having greater mobility than those of a more explanatory trial – for example, the variability of usual care over time – a future trial may wish to consider this approach to analysis.

4.2.2 Mixed methods for complex interventions

Santé-AF's structure, as a feasibility study for a pragmatic trial of two complex interventions, gave several imperatives for combining quantitative and qualitative methods at various stages of design and implementation. These are outlined and justified below.

This study accepts the definition offered by Creswell et al. in 2011, defining mixed methods as "employing rigorous quantitative research assessing magnitude and frequency of constructs and rigorous qualitative research exploring the meaning and understanding of constructs… intentionally integrating… these methods to draw on the strengths of each" (p.4).

The notion that the incorporation of a qualitative element into interventional studies strengthens such studies' credibility is not new: as early as the mid-1990s, researchers such as Sandelowski proposed that some of the practical value of what might now be called a pragmatic trial (Sandelowski referred to "real-life" investigations) could rest on qualitative lines of enquiry that modify and extend the "real-life" applicability of evidence (Sandelowski, 1996). Uptake of Sandelowski's proposal was slow; in 2019 Richards et al. found that the incorporation of a qualitative dimension in RCTs had become more widespread but that researchers analysed qualitative datasets separately and "miss[ed] opportunities to combine data in order to add rigour, enabling thorough and more complete analysis, provide credibility to results, and generate further important insights about the intervention under evaluation" (op. cit., p.1); the authors recommended full mixing of methods in most types of RCTs. In 2020, Fetters and Molina-Azorin advocated that a mixed methods design should be the "default approach" whenever interventional research is carried out, arguing for the value of adding qualitative inquiry to interventional designs in terms of maximising funding returns, understanding perplexing or null quantitative results, extending meaningfulness, and optimising interventions for target populations.

Specifically with regard to feasibility studies to inform investigational trials, mixed methods is an indispensable aid to interpreting quantitative findings, and formulating remediatory strategies for infeasibility (Feeley and Cossette, 2015; O'Cathain et al., 2015; Verhoef et al., 2005). "Applying binary indicators of feasibility [i.e., quantitative measures]," point out Aschbrenner et al. (2022), "provides limited information about *why* aspects of intervention or study procedures were or were not feasible" (2022, p.2; my emphasis).

Similarly, answering the "why" questions raised in complex intervention investigations, it is clear that the theory-based perspective on interventional research proposed by the NIHR Framework implies a mixed methods approach, which adds efficiency by understanding the *why* of "what works, for (and by) whom, and under what circumstances" (Skivington et al., 2021b). As Borglin points out, mixed methods can build in "feedback loops" in which knowledge from one methodological strand can inform another (Borglin, 2015). The Framework is in step here with earlier concepts of *context* put forward by methodological researchers considering qualitative approaches in a trials context: for instance, Hesse-Biber gives persuasive case study examples demonstrating the importance of "the context of discovery" in a trial, and how qualitative attention paid to the context will enhance "the overall credibility of RCT evidence" (Hesse-Biber, 2012). More recently, Noyes et al. noted that

mixed methods synthesis is helpful in understanding the impact of complexity on interventions – in particular, providing a means for emergent responses or findings that may not be predicted in advance, and therefore allowed for, by quantitative methods (2019).

For individualised holistic therapies in particular, mixed methods – particularly qualitative methods – may help to support the understanding of particular effects for individual participants:

> The drug or treatment might... not work for everyone. Conversely, a drug or treatment might... still work for some people. Qualitative inquiry at the individual level is needed to understand these individual-level differences (Johnson and Schoonenboom, 2016, p.589)

Trials that are more pragmatic than explanatory are also well-served by the synthesis of quantitative and qualitative methods (Creswell and Plano Clark, 2018) as this allows input of various stakeholder perspectives regarding the real-world effects of an intervention (Aschbrenner et al., 2022). Hunter and Armour (2019) argue that qualitative evidence is crucial to understanding the value of the intervention in terms of outcomes that matter to patients, including safety, access to interventions, and beliefs and preferences – an objective that overlaps strongly with pragmatic approaches to trials (Loudon et al., 2015). Creswell et al. (2011) align mixed methods with pragmatism in trials by defining the former as "focusing on research questions that call for real-life contextual understandings, multi-level perspectives, and cultural influences" (p.4) (a definition that also nods in the direction of complexity).

4.3 Feasibility study methodology

To identify methodological guidance for pilot and feasibility studies, a focused systematic literature search was carried out in October 2020 based on methods proposed by Wright, Golder and Rodriguez-Lopez (2014). The methodological review of feasibility study methods published by Hallingberg et al. (2018) was identified as a starting-point, and its 30 included papers were reviewed to determine those most relevant to Santé-AF as a feasibility study to inform a future pragmatic mixed-methods RCT of complex interventions (n=11). Forward citation searching was carried out on these papers, and on the Hallingberg paper itself (total n=12) using the Clarivate Web of Science citation index. Eligibility criteria included any paper critically discussing the philosophy, theory, methodology or methods of feasibility studies preparatory to a future trial. Exclusions were made for papers that only applied the methodology (i.e., pilot/feasibility studies themselves), and those without methodological relevance to Santé-AF (e.g., papers focused on cluster randomised pilots, placebo-controlled pilots, etc). 2,779 papers were retrieved, of which 408 were duplicates; title and abstract screening of the remaining 2,371 papers gave 203 papers for

full-text screening, of which 62 were included in the final selection alongside the original 12 derived from Hallingberg et al. (a total of 74 papers in all). This search was updated in June 2023, adding a further 30 studies to the total (n=104). For a list of these studies, see **Appendix A**, Miscellaneous section.

The selected literature largely consists of reviews of current practice in feasibility and pilot studies, and predictably therefore takes a practice-based focus, typically "when such studies should be undertaken, questions they should answer, suitable methods, criteria for deciding whether to progress to an effectiveness study and appropriate reporting" (Hallingberg et al., 2018, p.1). Although best practice is described and discussed, a rationale for "best" practice (other than that it is current and sometimes widespread) is not often offered, and few papers discuss theoretical foundations. One exception is the paper by Sekhon, Cartwright and Francis (2017) (which also notes the paucity of theoretical-level guidance in feasibility work); the paper theorises the specific construct of intervention acceptability, and its proposals were taken into account when designing Santé-AF's questionnaires and interview topic guides.

Two notable papers engaging with the theory of feasibility studies are a conceptual framework of pilot and feasibility studies (Eldridge et al., 2016b), and the further development of this framework (Bond et al., 2023). Both frameworks provide theoretically-focused guidance for use in designing feasibility studies; this includes a recommendation to use a range of methodologies including qualitative explorations, and the framing of feasibility investigations as iterative because the elimination of uncertainty – or at least its reduction to workable proportions – may require sequential attempts. Bond in particular considers the effect of current (UK) research funding practice on the conduct of pilot and feasibility studies; as the authors note, "pragmatism may often over-ride methodological reasoning and scientific principles" (p.6), with study design influenced by the preferences of senior researchers and funding award practice. Ultimately, there is a need to balance the elimination of uncertainty against "a pragmatic need for efficiency and value for money" (p.8). Similar themes are touched upon by Morgan et al. (2021) who comment that many feasibility studies may be redundant and therefore add waste to research; and Brown et al. (2019), who turn the research waste argument on its head: "An emphasis on high-quality pilot and feasibility studies may result in fewer but higher-quality large randomized trials and more efficient science" (p.1230).

The design of Santé-AF was guided by both conceptual frameworks. Other papers identified in the focused search, above, were used specifically with regard to setting feasibility objectives. For the final list of feasibility objectives, see **5.2.3**.

4.3.1 The role of feasibility studies in investigating complex interventions

There is a considerable literature focused on the role played by feasibility studies in investigating complex interventions, beginning with all iterations of the MRC/NIHR guidance published between 2000 and 2021. Much of this literature relates to the complex intervention as envisaged by the MRC/NIHR guidance, i.e., a pre-designed, often novel, composite intervention with a pre-defined level of adaptability. In such a case, the pilot/feasibility study investigates the interaction of components with each other, and the interaction of the intervention with the wider context of delivery (Skivington et al., 2021b; Bond et al., 2023), and it is clear that, for a novel intervention, testing these aspects is a key step to reducing the uncertainties associated with the intervention. For the established therapies investigated by Santé-AF investigating the interaction of therapeutic elements with each other could be thought less relevant. However, investigating the interaction of the therapy as a composite whole with various contexts (including the complex adaptive systems of the patient and the practitioner, and the overarching trial processes) was very much the focus of this feasibility study.

Scrutiny of the literature identified to set feasibility objectives for Santé-AF (**Appendix A**, Miscellaneous section) revealed some issues specific to complex interventions that were incorporated into Santé-AF's design. Giangregorio and Thabane (2015) suggest that a key issue to test in a feasibility study of a complex intervention is the willingness of healthcare providers to adhere to study protocols (in the case of Santé-AF, the practitioners and the scope of practice respectively). Similarly, Feeley and Cossette (2015) identify a number of complex-intervention-specific elements that should be investigated in feasibility studies, including whether the complex intervention can be delivered as planned, in a range of settings; and issues of contamination. These issues were included in the scope of Santé-AF's feasibility objectives.

4.3.2 Definition of Santé-AF as a feasibility study

Across the current literature, the terms *pilot* and *feasibility study* are often used interchangeably, and the respective definitions are the subject of ongoing clarifications (Bond et al., 2023). Terminology varies, despite actual process remaining broadly similar: the literature is scattered with pilot or feasibility *work*, *trials* and *studies*, and other terms such as *vanguard studies, exploratory studies* or *formative evaluation*, applied variously to questions of clinical, procedural or methodological feasibility (Lowe, 2019; Hallingberg et al., 2018; Morris and Rosenbloom, 2017; Abbott, 2014; Giangregorio and Thabane, 2015; Whitehead, Sully and Campbell, 2014; Arain et al., 2010).

Eldridge et al.'s formal consensus study, carried out in 2016, concluded that mutually exclusive definitions were "neither necessary nor desirable" (Eldridge et al., 2016b, p.17), and defined

feasibility as an overarching concept exploring those aspects of a research project that require more information before the project can progress. In 2023, a related team of authors named this required information "the uncertainty" (Bond et al., 2023, p.3) and proposed that the level of uncertainty is a key factor in deciding whether a feasibility study or a pilot study is required: higher levels of uncertainty about individual trial elements call for feasibility investigations, while pilots should be chosen in cases where there are lower levels of uncertainty about the individual trial elements. In the latter case, the focus shifts to include the uncertainty associated with the *integration* of those individual trial elements.

Santé-AF follows this guidance in defining itself as a feasibility study rather than a pilot trial, due to the level of uncertainty associated with some feasibility elements including the acceptability of interventions, assessments and general trial processes, for practitioners, participants and Participant Information Centres (PICs). A small-scale trial was chosen as the vehicle for the feasibility study, as it offers an efficient, unified means of evaluating all major uncertainties associated with the research question.

A second reason for defining Santé-AF as a feasibility study was that, even had key elements' uncertainty levels been lower, it was not possible to investigate the *integration* of these elements (as per Bond et al.'s definition of the pilot trial approach) because some processes were fundamentally dissimilar to those that would be used in a future trial. For instance, in the feasibility study a sole researcher conducted study assessments using generic tools including the Microsoft Office suite; but in a large-scale trial, a team of assessors would typically conduct assessments with multi-user specialist tools for data capture and storage, an approach that would affect the integration of data collection with other trial processes such as data management and data analysis. This shift from feasibility to large-scale trial working processes would likely be mirrored across other areas, including communications, site set-up and management, and overall trial governance – all of which would substantially affect the degree of integration between aspects of the trial. The sole-researcher model is therefore unrepresentative of the processes of a future trial, and would not produce process-related findings that could be generalised to a future trial. This study is therefore described as a feasibility study.

4.3.3 Feasibility objectives in Santé-AF

Following the literature on pilot and feasibility studies, the design of Santé-AF took a strong practice-based focus. Working from both conceptual frameworks cited above, and the papers emerging from the focused literature search, 11 items were identified as common practice in feasibility studies, that would be relevant to Santé-AF. These were incorporated into the study's objectives (**5.2.3**).

Extra objectives were added to Santé-AF to investigate the feasibility of supplementary issues, including the acceptability of various study parameters to practitioners and PICs; the utility of the CardioSTAT® ECG monitors; and the feasibility of all objectives during the COVID-19 pandemic. This last objective was removed following the end of the pandemic in 2022, although the effects of the pandemic were included in analyses where relevant.

4.4 Philosophical foundations of Santé-AF

Mixed methods are thought to pose particular issues in terms of its informing philosophies because quantitative and qualitative research are each linked with different structural paradigms (Bressan et al., 2017). Holistic approaches to research suggest a relativist perspective on knowledge that in turn implies a constructivist approach, while reductionist methods broadly imply the post-positivist equivalent (Tashakkori, Johnson and Teddlie, 2020; Ghaemi, 2015).

Philosophically speaking, pragmatism positions knowledge as a product of the interactions between individuals and context. It is therefore both epistemologically constructed (subjective) *and* ontologically independent (objective), and the nature of reality is seen as a shared construct, the product of a complex, ever-evolving process (Shan, 2022; Harrits, 2011). The mixing of actual methods takes place at a more functional level: typically, theory, methodology, data collection and analysis techniques. At this functional level, then, methods are “a-paradigmatic” (Hall, 2013): essentially transparent, driven by sometimes contradictory paradigms as a set of tools deployed in the pragmatic service of specific research questions. At method level, there is no “either/or”; only a dialectically pluralist “both/and” which reverberates from method to paradigm to philosophy, driven by the requirements of the research question (Johnson and Schoonenboom, 2016).

In a pragmatic spirit, this chapter proposes reconciliatory strategies for two philosophical dichotomies – reductionism with holism, complexity with strategic simplification – embodied in the combination of constructivist qualitative with post-positivist quantitative methods. As demonstrated above, these reconciliatory strategies do not integrate the dichotomies; instead, they aim to hold each arm of the respective dichotomy in a productive tension, “to transform these tensions into new knowledge” (Creswell et al., 2011, p.4). In this way, the research question benefits from insights produced by each approach, and (in step with the complex investigations it investigates) supports the whole enquiry to become more than the sum of its parts (Regnault, Willgoss and Barbic, 2018).

5 Methods

This chapter sets out the methods used in the feasibility study, including adaptations made during the COVID-19 pandemic. Details are given of trial governance processes; study design including groups; allocation ratios and sample size calculation; and key trial parameters including eligibility criteria. The scope of each intervention and usual care is described. Methods used for study processes – including identification, recruitment, consent, randomisation, data collection and data analysis – are described and justified in relation to the research question and current literature. Finally, quantitative criteria specifying thresholds for progression to a future trial ("progression criteria") are devised and justified.

5.1 Design of a future large-scale trial

To define the parameters of a feasibility study, it is necessary first to define the future trial whose feasibility is being tested (Hallingberg et al., 2018). Following the evidence gap detected in **Chapter 3**, a future large-scale Santé-AF trial is anticipated to be a three-arm parallel randomised controlled pragmatic trial investigating "whole therapies" to answer the research question: What is the effect of acupuncture and nutritional therapy in addition to usual care for symptoms and HRQoL in people with AF?

Participants will be recruited from primary care settings and randomised to acupuncture + usual care, nutritional therapy + usual care, or usual care alone, on a 2:2:1 basis in favour of the intervention groups. Private practitioners of each therapy will deliver the interventions in routine clinical settings, following their standard scope of practice. Participants will be assessed at baseline, end of treatment and at least one longitudinal follow-up point. A range of quantitative and qualitative data on primary outcomes will be analysed and synthesised using mixed methods to produce a full understanding of the effect of each complex intervention on symptoms and HRQoL, including safety of the therapies. Nested studies using case study/case series methods will be incorporated to define the scope/flexibility of each complex intervention as delivered, and to investigate in depth the full effect of the two complex interventions for individual participants.

The feasibility study followed this design; however, it did not incorporate nested studies as described above. This omission was deliberately made, partly because such studies investigate methodological feasibility, which is beyond the remit of the current study's aim and research question (**5.2.1**, **5.2.2**); and partly for pragmatic reasons such as lack of thesis wordcount and time.

5.1.1 Pragmatism in Santé-AF

As demonstrated in **Chapter 3**, real-world evidence is scarce for individualised holistic therapies in the treatment of AF. The design of a future trial would therefore take a highly pragmatic approach, to generate "real-world" highly generalisable evidence regarding the effectiveness of both therapies in routine practice adjunctive to standard care, on outcomes that matter to AF patients, clinicians and policymakers (Zuidgeest et al., 2017a).

Routine practice requires taking into account the "total effects" of an intervention, including extraneous or non-specific effects arising from a lack of blinding (Schwartz and Lellouch, 2009) and especially where non-specific effects may influence patient outcomes (Zuidgeest et al., 2017a). Non-specific effects of both acupuncture and NT may include elements such as the patient-practitioner relationship, the consultation process including elements such as focused attention and empathy, treatment expectation, and patient characteristics such as optimism or spirituality (Greco et al., 2016; Prady et al., 2015, 2013). In a real-world context, the patient's awareness of their engagement with treatment, and any behaviour modifications or treatment expectations, are one element in the overall "package" of treatment effects (Zuidgeest et al., 2017b) and the holism of the intervention is poorly served by an attempt to isolate constituent elements, even if it were practical to do so (Paterson and Dieppe, 2005).

Having identified the pragmatic approach as appropriate, a secondary rationale was identified in the "striking commonalities" that exist between complexity and pragmatism (Long, McDermott and Meadows, 2018), and the suitability of the pragmatic approach to accommodate at least some of the complexities of individualised holistic therapies. A future large-scale version of Santé-AF was therefore designed as a more pragmatic trial following the framework set out in the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS-2) (Loudon et al., 2015).

Figure 5 (overleaf) shows the Santé-AF feasibility study described in terms of the PRECIS-2 "pragmascope". Rationale for the scoring decisions in each domain is given in more detail below. Chan et al. (2021) modified the PRECIS-2 tool for the purposes of pilot/feasibility studies; unfortunately this modified tool was published after Santé-AF had begun to recruit. See **5.14.8** for an outline of how Chan et al.'s modifications to PRECIS-2 were applied to the feasibility study during data analysis.

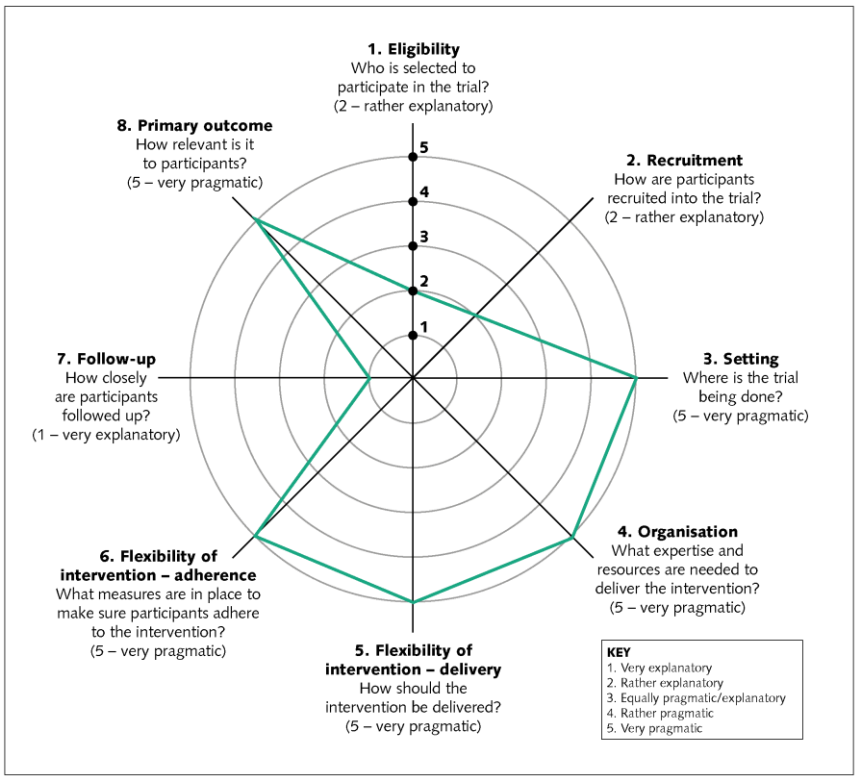

Figure 5: PRECIS-2 "pragmascope" for Santé-AF

Domain 1: Eligibility: This domain was scored as 2, “rather explanatory”. Some eligibility criteria (age, type and frequency of AF, perceptibility of symptoms, and familiarity with computers/video conferencing software) rendered the study population less representative of the general AF population than might be expected in a pragmatic trial.

Domain 2: Recruitment: This domain was scored as 2 (“rather explanatory”) because the recruitment path was highly structured, using communication methods that are not part of usual care. This was an ethical necessity, as neither researcher nor practitioners were part of patients’ direct care team and confidentiality was maintained until the patient had given permission to approach (NHS Health Research Authority, 2023).

Domain 3: Setting: This domain was scored as 5 (“very pragmatic”) as intervention settings for all three arms of the study were identical to those in routine practice.

Domain 4: Organisation: This domain was scored at 5 (“very pragmatic”). In all arms of the study, the resources, provider expertise and organisation of care delivery were identical to those in routine delivery.

Domain 5: Flexibility of intervention – delivery: This domain was scored at 5 ("very pragmatic"). There was considerable flexibility within the scopes of practice, as determined by the practitioner's clinical and professional judgement; and practitioners were allowed to deviate from the scope if, in their clinical judgement, the deviation was justified and safe. Nutritional therapists' scope of practice was limited by the study budget, which prevented full use of the NT "toolkit" (specifically, supplements and functional testing were unaffordable). However, in routine practice these elements may be excluded in any case, depending on the patient's personal financial constraints, so these exclusions were likely to produce a form of nutritional therapy perhaps not too dissimilar to that of routine practice.

Domain 6: Flexibility of intervention – adherence: This domain was scored at 5 ("very pragmatic") because adherence encouragement was no more than usual in routine delivery of either intervention.

Domain 7: Follow-up: This domain was scored at 1 ("very explanatory") because all patient-related data collection events were separate from intervention delivery and somewhat intensive, therefore potentially reducing pragmatism. This was unavoidable:

- Practitioners were not asked to collect at least a proportion of data directly from participants, meaning participants had to engage separately with the study for data collection purposes;
- The COVID-19 pandemic required assessments to be held online to minimise the risk of infection, which added to burden/intensity;
- There was a requirement to collect extra data for feasibility purposes, introducing extra burden/intensity for participants over and above that of a large-scale trial.

Domain 8: Primary outcome: This domain was scored at 5 ("very pragmatic"). The two primary outcomes for a future large-scale trial were specified as symptoms and HRQoL, which were considered the most important by Santé-AF's PPI panel.

Domain 9: Primary analysis: This concerned the extent to which all data was included in the analysis, and so was excluded as irrelevant to a study focused on feasibility rather than effectiveness outcomes (Chan et al., 2021).

5.1.2 Mixed methods in Santé-AF

To help design Santé-AF using mixed methods at appropriate stages and levels, the 2015 guidance on mixed methods by O'Cathain et al. was used. Broadly, the research question was taken as the pragmatic determinant of methodologies (Bishop, 2015), and the individual research questions posed at objective level likewise guided the choice of methods; equal value was ascribed to

knowledge derived from quantitative ("objective") and qualitative ("subjective") means (Drabble and O'Cathain, 2015; Creswell et al., 2011). The 2015 guidance was applied in the following areas:

- **Research questions:** A full range of feasibility questions was considered, and within this, those best addressed by mixed, qualitative and quantitative methods were identified;
- **Design and data collection:** A range of mixed, qualitative and quantitative methods was used;
- **Analysis:** Analysis was focused on a number of feasibility issues, set out in the objectives.

Santé-AF used a concurrent approach to mixed methods, in which quantitative and qualitative data were collected simultaneously and merged during analysis (Yardley and Bishop, 2015; Fetters, Curry and Creswell, 2013) to produce a synthesised view of feasibility objectives. The concurrent approach was chosen over asynchronous methods to minimise participant burden during data collection. Qualitative data was collected using questions similar to those in quantitative scales, to facilitate the merging process and to add depth to an understanding of quantitative data. Data was reported using joint display tables as a method of synthesis at individual domain level (Guetterman, Fetters and Creswell, 2015).

5.2 Feasibility study: rationale and description

A feasibility study is carried out primarily to reduce the uncertainty associated with a large-scale trial (Bond et al., 2023; Thabane and Lancaster, 2018; Eldridge et al., 2016b). By investigating key elements of feasibility, preliminary studies allow informed decisions regarding whether, and how, to proceed to a future large-scale trial (Hallingberg et al., 2018; Moore et al., 2018) and may provide important data to inform the parameters of a future trial (Avery et al., 2017); they may also increase efficiency of a future trial and improve its internal validity (Kistin and Silverstein, 2015). In providing the data required to take such a decision, feasibility studies reduce research waste (Zheutlin et al., 2020), promote research integrity (Wager, 2015), limit safety risks to participants (Morgan et al., 2021), and result in fewer and more efficient large-scale trials that are less likely to take up scarce resources and waste the time and hopes of their participants (Brown et al., 2019; Glasziou and Chalmers, 2018; Eldridge et al., 2016b).

A feasibility study approach was adopted for Santé-AF as a means of reducing the uncertainty of key parameters, and to allow a decision to be taken regarding whether, and how, to progress to a future trial. Generalisability in a feasibility or pilot study is generally interpreted as the applicability of study parameters to the future large-scale trial (Eldridge et al., 2016b); this feasibility study is

therefore an investigation of generalisability in these terms, but where relevant the study additionally considered the generalisability of a future trial to real-world contexts.

5.2.1 Research question for the feasibility study

The research question for this feasibility study is:

Is it feasible to carry out a future large-scale trial to investigate the effect of acupuncture and nutritional therapy for symptoms and HRQoL in atrial fibrillation?

5.2.2 Aim of the feasibility study

This feasibility study aims to reduce the uncertainty associated with elements of a future large-scale trial's design. These elements are set out below, as objectives.

5.2.3 Objectives of the feasibility study

The list of feasibility objectives tested by Santé-AF was informed by a small-scale survey carried out to determine the objectives tested by similar studies. For this survey, a search of MEDLINE was conducted to retrieve studies carried out between 2014 and 2020 that were similar to Santé-AF according to the PICO Population and Intervention domains (Richardson et al., 1995). Four categories were identified:

- **Feasibility studies** (P = AF/arrhythmia; I = self-management) (n=2);
- **AF trials** (P = AF; I = self-management/exercise) (n=5);
- **Acupuncture trials** (P = similar/AF comorbidity; I = acupuncture) (n=5);
- **Diet trials** (P = similar/AF comorbidity; I = diet/nutritional intervention) (n=3).

Details of objectives from the identified trials were extracted and tabulated (**Appendix A**, Miscellaneous section), and a core list of objectives was formulated for Santé-AF, each made up of a number of constituent domains. One bespoke objective was added (objective 6: Utility of CardioSTAT® monitor), and after the start of the COVID-19 pandemic, extra domains were added to various objectives to investigate the effect of the pandemic on feasibility. The final list of objectives, and the constituent domains, is shown in **Table 15** (overleaf).

Table 15: Objectives of the feasibility study

Objective	Objective components
Objective 1: Participants' willingness to take part	a) Participants' reasons for deciding to participate b) Participants' reasons for declining to participate c) Number of participants randomised from the total eligible d) Effect of the pandemic on willingness to participate* e) Practitioners' willingness to participate f) Effect of pandemic on practitioners' willingness to participate* g) PICs' willingness to participate h) Effect of pandemic on PICs' willingness to participate*
Objective 2: Appropriateness of eligibility criteria	a) Number of participants excluded by each eligibility criterion b) Similarity of participant characteristics to other AF studies** c) Effect of extra eligibility criteria added due to the COVID-19 pandemic* d) Number of practitioners eligible and reasons for non-eligibility
Objective 3: Participant retention	a) Percentage of consented participants retained at baseline b) Percentage of randomised participants retained at follow-up c) Number of compliance prompts needed, and quantity of data returned in response to each prompt** d) Participants' reasons for withdrawal e) Participants' reasons for remaining in the study f) Effect of the pandemic on participant retention*
Objective 4: Intervention acceptability	a) Participant satisfaction with group allocation b) Participant rating of intervention acceptability c) Effect of the pandemic on acceptability of interventions*
Objective 5: Acceptability of study assessments	a) Completeness of data returned by participants b) Acceptability of study assessments c) Effect of the pandemic on the acceptability of study assessments*
Objective 6: Utility of CardioSTAT® monitor	a) Correlation between symptom diaries and CardioSTAT® data b) Influence of CardioSTAT® on decision to participate and stay in study c) Effect of the pandemic on utility of CardioSTAT® monitor*
Objective 7: Experience of study participation	a) Participants' experience of study participation b) Effect of the pandemic on participants' experience of study participation* c) Practitioners' experience of study participation d) Effect of the pandemic on practitioners' experience of study participation* e) Practitioners' experience of intervention fidelity

* not treated as a separate domain in the final analysis. Results are incorporated with the relevant domain listed above

** analysis was conducted but was judged not to be useful for a future trial. Results are reported in Appendix D for completeness

5.3 Trial set-up

Figure 6 shows a timeline of the study's key events along with the events affecting study progress during the COVID-19 pandemic (Institute for Government, 2022; NHS England, 2020).

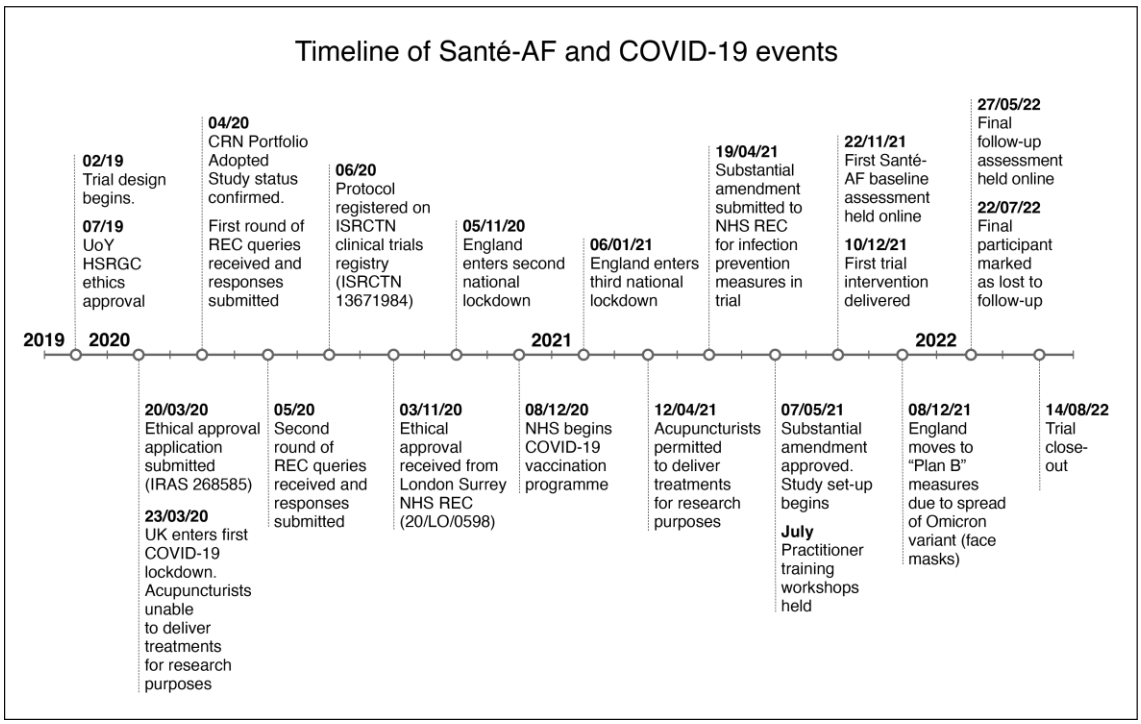

Figure 6: Timeline of trial and COVID-19 events

Study design began in 2019. In July 2019 the study gained ethical approval from the University of York Department of Health Sciences Research Governance Committee (HSRGC/2019/346/H). In March 2020 the study protocol was submitted for Health Research Authority (HRA) ethical approval via the Integrated Research Application System (IRAS Project ID 268585); this included an application for Portfolio Adoption by the NIHR Clinical Research Network (CRN), which was confirmed in April 2020. Two rounds of queries were received from the London Surrey REC (reference: 20/LO/0598) in April and May 2020; the REC provided a favourable opinion and HRA approval was received in November 2020. All documents can be found via **Appendix A**, Protocol and ethics section.

The COVID-19 pandemic prevented all acupuncturists on the study from delivering non-urgent treatments, including treatments for the purposes of research, between March 2020 and April 2021 (Bovey, 2021; British Acupuncture Council, 2021). The continuing delay was used to modify study processes to mitigate the risk of COVID-19 transmission. Following the lifting of restrictions on acupuncturists in April 2021, the study moved into its set-up phase.

The Trial Steering Committee was established in April 2021; members signed a Terms of Reference document to accept their responsibilities in May 2021 (**Appendix A**, Trial Steering Committee section). Between May and June 2021, the National Institute of Health Research Clinical Research Network (NIHR CRN) and HRA processes for study set-up were initiated.

Eligible practitioners were identified, recruited and trained in the study processes between May and July 2021. In August 2021, the Yorkshire & Humber branch of the CRN sent Expressions of Interest (EOIs) to Vale of York GP practices, inviting them to act as Participant Identification Centres (PICs).

Between September and November 2021, completed EOIs were received from four GP practices. Site set-up was carried out, including a virtual Site Initiation Visit (SIV) for each. Completed search and screening logs were returned to the researcher identifying the number of eligible patients, and permission-to-approach (PtA) packs were delivered to each PIC in October/November 2021, for personalisation and forwarding to potential participants.

Participant baseline assessments began in late November 2021, with the first study intervention delivered on 10 December. The final follow-up assessment was held in May 2022, with trial close-out in August 2022.

5.3.1.i Changes made to the study due to COVID-19

This section reports the "important modifications" made to the feasibility study due to COVID-19 (Orkin et al., 2021):

1. Study assessments were redesigned to be conducted online;
2. Nutritional therapists were required to hold consultations online;
3. Acupuncturists were required to follow the BAcC code of COVID-19 safety;
4. A small amount of extra data was collected from participants regarding COVID-19 status and attitudes;
5. Three extra eligibility criteria were added to recruit participants who were able to work online;
6. A longer follow-up was removed, as it was no longer feasible due to delays caused by lockdowns;
7. The Trial Steering Committee (TSC) monitored levels of COVID-19 in the York area and was empowered to pause the Acupuncture group when predetermined thresholds were breached if, in their collective judgement, it would be unsafe to continue.

Modifications were planned by the researcher, reviewed by academic supervisors and the University of York's sponsor representative, and approved by the London Surrey REC and the HRA (NHS Health Research Authority, 2021b). A modification timeline is given in **Figure 6**.

The original study protocol was modified to include an objective looking at the feasibility of all objectives during the COVID-19 pandemic (**Appendix A**, Protocol and ethics section). However, unless a future trial were to take place under similar conditions, this objective was judged not to be useful and was therefore removed as a separate objective; progression criteria were not applied. Where the COVID-19 pandemic influenced feasibility, this was included in data analysis and the results are reported in **Chapter 6**.

5.3.1.ii Patient and public involvement (PPI)

During the design phase, a panel of two people with AF and one lay person advised on issues including:

- Outcomes likely to be of importance to people with AF;
- Choice and development of measurement instruments including the Interview Topic Guides;
- Participant burden;
- Issues of dignity, privacy, confidentiality and study-related wellbeing.

The panel was consulted once at the start of the study design period, and once before the end. Advice was incorporated into study design and documentation.

5.3.1.iii Trial Steering Committee

As interventions on the Santé-AF study were delivered privately (externally to the National Health Service (NHS)), the study protocol approved by the HRA Research Ethics Committee (REC) (**Appendix A**, Protocol and ethics section) made provision for a Trial Steering Committee (TSC) to take responsibility for participant safety in lieu of the more usual oversight from an NHS Research and Development (R&D) department.

The Santé-AF TSC comprised five members:

- A chair with research and trials expertise;
- An expert acupuncturist member;
- An expert nutritional therapist member;
- An expert cardiologist member;
- The researcher.

The remit of the TSC was set out in a signed Terms of Reference document. Responsibilities were more limited than those of a regular TSC, since the responsibility for scientific integrity and study process was devolved to the researcher's academic supervisors. Instead, the Santé-AF TSC

focused on participant safety (particularly with respect to COVID-19) and consideration of any new information of relevance to the study's research question and topic.

The TSC met immediately before the active intervention period began (10/11/21) to discuss whether to pause the Acupuncture group of the study in view of COVID-19 incidence in the local area. A second meeting was held by correspondence to oversee the handling of an apparent adverse reaction in the NT arm of the study.

All documents can be found in **Appendix A**, Trial Steering Committee section.

5.3.1.iv Therapy Advisory Panels

Two Therapy Advisory Panels were convened to inform this feasibility study, comprising senior acupuncturists and nutritional therapists. The panels were responsible for advising on the following study elements:

- ascertaining clinically contraindicated practice for AF patients in each therapy and overseeing the incorporation of this into the therapy-specific study manuals to which study practitioners were contractually obliged to adhere;
- helping to define adverse events related to the therapies;
- supporting safety and ethical compliance, together with best and routine practice, within each therapy's codes of professional conduct.

5.4 Allocation ratio

Randomisation used an unequal allocation ratio of 2:2:1 in favour of the active intervention groups. In a future trial investigating effectiveness, differences in effect size between each intervention and the Usual Care group may be larger than the differences between the two interventions, and the allocation of increased power to the two intervention groups may therefore be helpful in maximising the ability to detect any differences in effect size between them at follow-up (Chandereng, Wei and Chappell, 2020; Sverdlov and Ryeznik, 2019; Dunnett, 1955). Additionally, given the complex nature of the interventions and populations, and the number of potential variables associated with each, maximising power to the intervention groups allows for a more robust investigation of specific covariates within and between groups.

The final reason for maximising the power of the intervention groups in this feasibility study was the relative lack of safety data for nutritional therapy. The unequal allocation provided increased power to detect any adverse events associated with nutritional therapy (Gupta et al., 2021c; Hey and Kimmelman, 2014).

5.5 Sample size calculation

Many sources suggest that a formal sample size calculation is not required for a feasibility or pilot study (Eldridge et al., 2016b; Billingham, Whitehead and Julious, 2013); others suggest figures such as 12 participants per group as "a good round number… [that] facilitates the setting of a variety of block sizes" (Julious, 2005, pp.287–288). Viechtbauer et al. (2015) offer an approach based on a goal of problem detection, proposing a formula to detect any problem with an estimated probability of occurrence, at a preferred confidence threshold. But the authors' formula allows sample size to be calculated on the predicted incidence of only one type of problem, whereas feasibility studies typically investigate multiple feasibility objectives. Finally, Lewis et al.'s method (published in 2021, after this study was designed) is based on hypothesis testing for each of the progression criteria; this would have been infeasible for Santé-AF, principally because even conservative feasibility thresholds estimated using this method yielded a sample size approximately three times that of Santé-AF, which would have been impractical for a sole-researcher study and exceeded the study's budget (Lewis et al., 2021).

For this feasibility study, a sample size was calculated on the basis of Cocks and Torgerson's one-sided confidence interval approach (2013). This uses:

1. **A one-sided 80% confidence interval.** A one-sided CI is specified on the basis that a future large-scale trial will not take place if there is evidence of harms associated with the interventions, and therefore a two-sided CI is redundant. An 80% power level gives a reasonable compromise between the power of the feasibility study on the one hand, and on the other, the time, costs and potential ethical issues of carrying out the study;
2. **The proposed sample size of a future trial**, which in this case was calculated using the Atrial Fibrillation Effect on Quality of Life (AFEQT) disease-specific HRQoL scale (Spertus et al., 2009) as a primary outcome; AFEQT was considered the most appropriate single measure for sample size calculations due to its measurement of both symptoms and HRQoL.

5.5.1.i Sample size calculation for a future large-scale trial

As demonstrated in **Chapter 3**, there are no controlled trials of acupuncture or nutritional therapy investigating changes in AF-related HRQoL or symptoms that are of sufficient quality to guide a sample size calculation for a future trial. It is therefore not possible to identify a relevant between-groups difference at follow-up.

Spertus et al. determined that the within-group change (n=66) in mean scores for the AFEQT questionnaire at 3 months following pharmacological therapy was 9.8 points (9.8%), and the corresponding standard deviation was 20.0 (Spertus et al., 2011). To detect this effect size at a

power of 80% with a significance level of 5% requires a sample size of 66 participants per group. Adjusting this for three groups gives a total sample size of 198 participants; adjusting again for an estimated 20% loss to follow-up (Close et al., 2016) gives 238 participants in total (Sealed Envelope Ltd, 2012; Julious, 2004). Rounded to 240 for convenience and allocated to groups this gives a ratio of 96:96:48.

However, Spertus et al. calculated this difference within participants (i.e., a difference in AFEQT score between baseline and follow-up for each participant). In the absence of any between-groups AFEQT differences to be derived from the literature, the above sample size calculation is based on the assumption that the same magnitude of difference is feasible between groups at follow-up as within participants over time. This point is discussed further in **7.9**.

5.5.1.ii Sample size calculation for the feasibility study

Applying Cocks and Torgerson's CI-based approach to the standardised effect size derived from Spertus et al.: the feasibility study sample size at 80% power and a 5% significance level was calculated as ≈24 participants across three groups. Adjusting for 20% attrition gave 29 participants (rounded to 30 for convenience). Adjusting again for the 2:2:1 allocation ratio in favour of the intervention groups gave a per-group total for the feasibility study of 12:12:6.

5.6 Eligibility criteria

Santé-AF set out eligibility criteria for participants and practitioners. Because the interventions in Santé-AF were delivered by private therapists, practitioners were considered as a type of participant in order to investigate a number of feasibility objectives relating to their participation.

5.6.1 Eligibility criteria (participants)

Table 16 (overleaf) shows participant eligibility criteria with justifications. These were amended in April 2021 to protect participants vulnerable to COVID-19; this added inclusion criteria 6–7, and exclusion criterion 11.

Table 16: Eligibility criteria for participants

#	Inclusion criteria (participants)	Justification
INC1	Aged ⩾ 45 and ⩽70	Age range with greatest prevalence of AF
INC2	Diagnosis of AF ⩾ 6 months and ⩽ 60 months previously	To coincide with an anticipated 'settling in' post-diagnosis period in which conventional treatment has become stable
INC3	Stroke prevention measures offered/applied where indicated	To reduce risk of stroke (National Institute for Health and Care Excellence, 2021) and maintain safety of study participants
INC4	Self-detectable paroxysmal atrial fibrillation of at least weekly frequency	Necessary to reliably complete 7-day self-report diary
INC5	Owner of, and able to use, a mobile phone	For study communication and compliance prompting
INC6	Home broadband of sufficient capacity to sustain NT appointments and study assessments	For nutritional therapy appointments (if allocated to this group) and online study assessments
INC7	Owner of, and able to use, a device capable of video-conferencing OR happy to use study iPad	For online study assessments
INC8	Willing to have acupuncture or nutritional therapy alongside usual care, or usual care alone	To comply with intervention requirements
INC9	Willing to travel to attend appointments for acupuncture *(travel expenses subsidised)*	To attend acupuncture appointments if allocated to that group
INC10	Willing to wear a CardioSTAT® ambulatory ECG monitor (AED) for 7 days x 2 times over the course of approximately three months, then return in reply-paid envelope to the manufacturer for data analysis	To provide AF monitoring data
INC11	Speak/understand English well enough to engage meaningfully with interventions and assessments (researcher's judgement)	No budget to provide translation
INC12	Able to give informed consent	To comply with ethical requirements

#	Exclusion criteria (participants)	Justification
EXC1	Diagnosed with valvular AF	Type of AF is not amenable to study interventions
EXC2	Pacemaker, implantable defibrillator, neurostimulator, any other type of active implantable device	Contraindicated to CardioSTAT®
EXC3	Diagnosed with kidney disease levels 4 or 5	Contraindicated to nutritional therapy
EXC4	Diagnosed with terminal or severe illness	To reduce patient burden/reduce loss to follow-up due to illness
EXC5	Diagnosed with any blood clotting disorder	Contraindicated to acupuncture
EXC6	Diagnosed (including self-diagnosis) with any condition or disorder contraindicating suitable moderate exercise	Contraindicated to exercise
EXC7	Diagnosed (including self-diagnosis) with any eating disorder past or present	Contraindicated to nutritional therapy

Table continued overleaf

#	Exclusion criteria (participants)	Justification
EXC8	Pregnant or trying to conceive	For safety of pregnancy
EXC9	Currently taking part in other research rendering participant unable to have either intervention, or which is likely to affect study outcomes, or which renders it unsafe for participant to continue	For safety of participant and integrity of research
EXC10	Currently having, or have had in the last six months, a course of acupuncture or nutritional therapy	Avoidable confounding factor
EXC11	Classified as shielding, clinically vulnerable or clinically extremely vulnerable with regard to COVID-19, or living with or bubbled with anyone in any of these categories (National Health Service, 2022b)	To protect participant and household against increased risk of cross-infection with COVID-19
EXC12	Regularly using a TENS machine or receiving any kind of energy delivery therapy to the upper torso (diathermy therapy, diagnostic or therapeutic ultrasound, radiation therapy, electro-surgery or x-ray)	Contraindicated to CardioSTAT®
EXC13	Any other clinical reason why patient should be excluded, in the clinical judgement of the patient's GP	To protect patients

5.6.2 Eligibility criteria (practitioners)

Table 17 shows practitioner eligibility criteria. Criteria were altered in April 2021 to accommodate COVID-19 working practices, resulting in the addition of INC9–10.

Table 17: Eligibility criteria for practitioners

#	Inclusion criteria (practitioners)	Justification
INC1	Qualified to minimum BSc level in either therapy	To assure quality of interventions and congruence with practising base of practitioners
INC2	Minimum of three years' post-qualification experience in continuous active practice	To assure quality of interventions
INC3	Full member of the relevant professional body (British Acupuncture Council or British Association of Nutritional Therapy and Lifestyle Medicine)	To assure a level of professional and ethical conduct
INC4	Full professional insurance, and undertaking to maintain such insurance for a minimum of one year after the end of active involvement with the study	To provide intervention-related indemnity; to maintain insurance in case of post-treatment claims
INC5	Possessed of any necessary local regulatory permits	To ensure interventions are meeting applicable byelaws
INC6	(Acupuncturists only) Operating with a current waste disposal contract including the provision of Duty of Care notices for contaminated sharps disposal	To ensure intervention is meeting applicable law
INC7	Willing and able to engage with study procedures and parameters of practice, including training (as set out in practitioner eligibility questionnaire)	To meet study requirements
INC8	[Acupuncturists only] Premises within five-mile radius of York city centre	To minimise travel burden for participants

Table continued overleaf

#	Inclusion criteria (practitioners)	Justification
INC9	[Acupuncturists only] Willing to abide by the COVID-19 practice guidelines set out by the British Acupuncture Council	To maintain COVID-19-related safety for participants
INC10	[Nutritional therapists only] Willing and able to hold all consultations and participant contact by online methods only	To maintain COVID-19-related safety for participants

#	Exclusion criteria (practitioners)	Justification
EXC1	Any unresolved fitness-to-practise, professional conduct, legal, ethical or disciplinary issues	To avoid bringing the study into disrepute

5.7 Recruitment

Santé-AF investigated the feasibility of recruiting both participants and practitioners.

5.7.1 Recruitment (participants)

5.7.1.i Identification of eligible patients

The majority of patients with AF are managed in a primary care setting (Ponamgi et al., 2021), so this was the starting-point for participant recruitment. Four primary care practices in the York area were recruited by the Yorkshire & Humber branch of the NIHR Clinical Research Network, and functioned as Participant Information Centres (PICs). Each PIC completed a database search and a subsequent screening process to identify participants on the basis of the eligibility criteria. This process was logged in each PIC's search/screen log (**Appendix A**, Participant identification and randomisation section), which produced a final number of patients eligible according to the medical record.

As the researcher was not part of patients' direct care team and had no legitimate access to patients' medical notes, it was necessary to protect confidentiality until they had given permission to be informed about the study (NHS Health Research Authority, 2023). A "permission-to-approach" (PtA) process was therefore used to identify eligible patients (NHS Health Research Authority, 2020a).

5.7.1.ii Permission to approach

The required number of blank permission-to-approach (PtA) packs (**Appendix B**) was delivered to each PIC by the researcher; PIC staff addressed and posted a pack to each identified patient. The packs contained a covering letter, a double-sided A4 study information sheet, the PtA form itself, a

study-branded pen to maximise response rates in minimised timescales (Mitchell et al., 2021; Cunningham-Burley et al., 2020; Bell et al., 2016) and a reply-paid envelope.

PtA packs introduced the Study ID (SID) number, which pseudonymised participants for the duration of the study and was logged in a "look-up table" that linked participant identity with the SID. The look-up table was stored securely on UoY Department of Health Sciences servers. Although it was not possible to blind the researcher during the study, SIDs were used as the sole means of identifying the participant on all study documentation.

5.7.1.iii Informed consent and full eligibility check

Completed PtA forms were returned direct to the researcher at the study centre. The researcher posted a full participant information pack (**Appendix B**) to the patient containing a covering letter, the participant information sheet and two copies of a consent form, with a study-branded pen in a plastic wallet.

A phone call (the "queries phone call") was made to each patient 2-4 days after posting the full participant information pack. Patients were invited to ask any questions. If patients indicated willingness to take part after all questions had been answered to their satisfaction, they were asked to sign and return one copy of the consent form direct to the researcher. The queries phone call often acted as a reminder to the participant to return the consent form (Watson and Torgerson, 2006).

All patients returning a full, valid consent form were contacted by phone to arrange a screening call to determine full eligibility (**Appendix C**). This stage was originally necessary because the eligibility criteria require information that was not available via the patient's medical record (inclusion criteria 4-8; exclusion criteria 6-8, 10, 12). Unfortunately, errors were made during the search/screen process by one PIC, identifying a number of non-eligible participants; the researcher also received a query from a patient who was not a patient at a study PIC and had been passed the participant information pack by a friend. To maintain safety and study integrity, the screening call was modified to include a self-reported check on *all* eligibility criteria, including how the participant had received the information pack. This was the subject of ethical Amendment 3 (**Appendix A**, Protocol and ethics section).

The screening call was carried out at a date/time to suit the participant, including evenings and weekends. The call used a questionnaire to check all eligibility criteria, applied by the researcher who recorded all answers (**Appendix C**). In addition, where participants gave permission to be interviewed, the script included qualitative questions to determine suitability for interview and support the stratification for interview sampling.

Participants were informed of their eligibility during the screening call, and the baseline assessment appointment was also booked. Study eligibility was then subsequently confirmed by email and posted letter; this also contained confirmation of any sub-group allocation and a confirmation of the baseline assessment appointment, which was also confirmed and reminded by SMS text to the participant's mobile.

Data from the participant recruitment process was evaluated to answer objectives 1 (participants' willingness to take part) and 2 (appropriateness of eligibility criteria).

5.7.2 Recruitment (practitioners)

Informal discussions with acupuncturists and nutritional therapists in the researcher's networks, held in April 2021, suggested that four participants was the maximum a practitioner could comfortably accommodate (**Appendix A**, Miscellaneous section). The recruitment target for practitioners was therefore three practitioners per therapy, with each being allocated a maximum four participants. It was anticipated that any excess of eligible practitioners would trigger a random selection process.

To ensure a consistent standard of safe and effective practice, practitioners were identified in May 2021 via the online membership directories of the largest professional association for each therapy: the British Acupuncture Council (BAcC) and the British Association for Nutrition and Lifestyle Medicine (BANT) (British Acupuncture Council, 2023; British Association for Nutrition and Lifestyle Medicine, 2023). Practitioners therefore met HRA requirements for research by being "appropriately trained by qualifications and experience" (NHS Health Research Authority, 2017). Practitioner inclusion criteria 1, 3-6, and 8 were checked in membership directories (**Table 17**), and practitioners meeting the criteria were sent an invitation by email along with a brief study information sheet and a link to the full practitioner eligibility questionnaire online. Practitioners who completed the questionnaire and met the full eligibility criteria were checked with their respective professional body regarding the sole exclusion criterion in **Table 17**. The recruitment period ended with the commitment in principle of six practitioners by June 18th, an overall recruitment duration of three weeks.

The six eligible practitioners were legally bound to the study via a legal agreement with the University of York. Three half-day training workshops were held in July 2021 to induct practitioners into study processes; topics included the aetiology and pathophysiology of AF, confidentiality and data protection, safety, ethics, reporting, and a review of the scope of practice for each therapy. Workshops were supported by a therapy-specific study manual covering all study processes and setting out any restrictions on the scope of routine practice.

A range of qualitative and quantitative data was gathered during practitioner recruitment and evaluated to answer objectives 1 (participants' willingness to take part), 2 (appropriateness of eligibility criteria) and 7 (experience of study participation).

All documents can be found in **Appendix A**, Practitioner documents section.

5.8 Randomisation

The researcher enrolled participants and randomly allocated them to one of the three groups (Acupuncture, Nutritional Therapy (NT) and Usual Care). The process used a block design with a list length of 30 and block sizes of 5 and 10 randomly permuted to minimise the possibility of subversion (Broglio, 2018). Randomisation was carried out using the Simple+ randomisation facility (Sealed Envelope Ltd, 2021), which concealed allocation from the researcher until the point of assignment; allocation, which included the participant's unique study ID number, was confirmed by email (**Appendix A**, Participant identification and randomisation section).

To minimise attrition before the baseline assessment, it was originally intended to randomise participants after the assessment was carried out. However, the 33% of participants randomised to wear a CardioSTAT® ECG monitor was distributed on the same 2:2:1 ratio across the groups. It was therefore necessary to know the participant's allocation in advance of the baseline assessment so that they could be randomised within that group to the CardioSTAT® subgroup. Randomisation was therefore carried out before the baseline assessment and not revealed to participants until after the assessment had been carried out. Participants were notified of their group allocation by email and post once the baseline symptom diary had been received at the study centre.

Data collected during randomisation was evaluated to answer objective 1 (participants' willingness to take part).

5.8.1 Other allocations

Participants were allocated to the following subgroups within Santé-AF.

5.8.1.i Allocation to CardioSTAT® ECG monitor subgroup

Study funding did not allow for the allocation of a CardioSTAT® ECG monitor to every participant. It was also part of the study's feasibility objectives to assess the effect of the monitor on study participation (objective 6), and a non-CardioSTAT® control subgroup was therefore required in order to detect any differences between the subgroups.

One-third of the total participants (n=10) was allocated to wear a monitor at baseline and follow-up (allocated between groups on the same 2:2:1 ratio as for the overall randomisation). An Excel spreadsheet was used to generate simple random allocations within each group (**Appendix A**, Participant identification and randomisation section).

5.8.1.ii Allocation to interview subgroup

On the consent form (**Appendix B**), participants were asked to indicate their willingness to be interviewed on topics including their experience of AF, study participation and their allocated therapy (or usual care). During the screening call (**Appendix C**), a range of demographic data was obtained from all participants, and the subset willing to be interviewed were asked three questions regarding their experience of AF diagnosis, its effect on their daily lives, and their feelings about complementary therapy. Participants' responses were assessed by the researcher for willingness to communicate their personal lived experience, beliefs and opinions. This was analysed alongside demographic data also obtained during the screening call to inform a maximum variation sampling strategy (Palinkas et al., 2015), stratifying interview participants across four dichotomised variables:

1. Age: older/younger than 57 years;
2. Sex: male/female;
3. Duration of diagnosis: earlier/later than 33 months;
4. Previous experience of complementary therapies (little/none or moderate/extensive, where moderate/extensive was defined ≥ a course of one therapy in the previous five years).

Participants were sequentially assigned to the interview subgroup (n=16) if they matched the available maximum variation sampling criteria, and were willing to communicate about their lived experience.

5.8.1.iii Allocation to practitioner

Allocation to practitioners within each group aimed at four participants per practitioner (**5.7.2**) and was guided by an outline of participant availability determined during the screening call (**Appendix C**) which was matched with each practitioner's general availability. Participants and practitioners were each given the confidential option to decline the offered participant/practitioner without having to declare their reasons; this was intended to eliminate an avoidable confounding factor arising from any pre-existing relationship. It was envisaged that, in the case of declines, the researcher would nominate another practitioner within the group, based on both parties' availability.

5.8.2 Blinding

As a feasibility study investigating feasibility of a future pragmatic trial, Santé-AF used an unblinded approach (Zwarenstein, 2017). The behavioural nature of the interventions in Santé-AF did not allow for blinding of participants or practitioners (Weaver and Hodges, 2021); nor was it possible to blind the researcher, who carried out enrolment, randomisation and most of the assessment, and was therefore aware of group allocation throughout.

The single outcome assessor remaining unaware of participants' group status was Icentia Limited, supplier of the CardioSTAT® ECG monitor and the resultant data analysis services. Monitors and symptom diaries were returned direct to Icentia by participants, and were analysed without knowledge of the intervention received.

5.9 Definition and scope of interventions and usual care

The scope of interventions and usual care in the trial are described in this section.

5.9.1 Acupuncture

As part of the overall modality of Chinese medicine, acupuncture is thought to have originated in China between 100-200 BCE, being formalised as Traditional Chinese Medicine (TCM) by Mao (Gross, 2018) and popularised in the West after Nixon's visit to China in 1972 (Lu and Lu, 2013). Various styles of acupuncture exist including Western medical acupuncture, which adapts classical principles to modern medical theories (White, 2009); microsystems acupuncture, which maps a smaller area of the body (such as feet, scalp, hands) to the wider body to treat the entire organism (Federation of Holistic Therapists, 2021); and traditional acupuncture, which uses a conceptual model based on classical Chinese principles (Scheid, 2002).

Traditional acupuncture itself encompasses various styles including Five Elements, Stems and Branches and the Balance Method; the dominant style of traditional acupuncture in the West, and specifically in the UK, is known as Traditional Chinese Medicine (TCM) (Kaptchuk, 2012). TCM acupuncture is based on theories of qi (arguably best understood as "vital energy") and the rebalance of qi in a network of channels or meridians which incorporate mind, body and spirit in a holistic, integrated model based on the dynamic transformation and movement of energies known as the yin-yang model (British Acupuncture Council, 2023a; Yan, 2022).

The practice of TCM acupuncture involves the diagnosis of one or more *patterns of disharmony* according to TCM principles, using information gathered from patient consultation and observational techniques including tongue and pulse observation. Treatments centre around the

insertion of solid filiform needles into "acupoints" on the body. A number of sub-modalities are also practised, including cupping (using vacuum cups on the skin to address musculoskeletal issues); electroacupuncture (a low-intensity electrical current passed through inserted needles); guasha (scraping the skin to stimulate regenerative processes); moxibustion (burning the herb *artemisia vulgaris* close to the skin or on an inserted needle to stimulate regenerative processes); and tui na massage (a form of vigorous massage to address musculoskeletal issues) (British Acupuncture Council, 2023a).

Acupuncture's specific mechanisms of action (needling and sub-modalities) are thought to invoke modulation of sympathetic tone and motor reflexes, immune system activation, endogenous descending pain inhibitory and facilitatory systems, and activation or de-activation of limbic structures, hypothalamic-pituitary-adrenal axis, prefrontal and frontal cortices and parasympathetic activity amongst others (Lund and Lundeberg, 2016; Cheng, 2014; Kawakita and Okada, 2014). Stimulation of the vagus nerve via its auricular branch – a strategy within the scope of TCM acupuncture – reduces cardiac sympathetic activity and may promote parasympathetic activity, to which extent it is thought to have a cardioprotective function, and may reverse atrial remodelling and attenuate AF symptoms (Elamin et al., 2023; Liu et al., 2018; Li et al., 2015; Stavrakis et al., 2020; Stavrakis et al., 2015). The scope of acupuncture in the study was defined as the TCM style of acupuncture recognised and insured by the British Acupuncture Council (BAcC), and following a basic model set out in MacPherson and Schroer (2007). Traditional Chinese Medicine (TCM) is the form of traditional acupuncture most widely practised in the UK (British Acupuncture Council, 2009). (For clarity, it should be noted that in much complementary medicine research the phrase "traditional Chinese medicine" refers to what would more accurately be known as Chinese herbal medicine.)

In Santé-AF, the acupuncturists' scope of practice is set out in the acupuncturists' study manual (**Appendix A**, Practitioner documents section), comprising the following basic tenets:

- A prohibition on referral of participants to other complementary therapists, and provision of Chinese herbal medicine;
- An explicit reiteration of safe practice standards – particularly those relating to work with anticoagulated patients (British Acupuncture Council, 2018);
- A direction to follow usual practice when explaining treatment principles, advising on self-care/lifestyle or discussing TCM theory with participants.

In keeping with the pragmatic nature of the study, acupuncturists were advised that departures from the defined scope of practice were permitted if these could be justified in their clinical and professional judgement, which incorporates safety judgements. The acupuncturists' log book was used to capture any such departures.

Treatments were delivered at practitioners' clinics, which were required to be within a five-mile radius of the York Teaching Hospital. Travel expenses were subsidised by the study, with practitioners giving £5 in cash at each attended appointment. Participants were asked to contact the acupuncturist to arrange appointments at suitable times. Practitioners were asked to regard a treatment regime of once-weekly treatments over eight weeks as a desirable standard, but were given flexibility to vary this within a 10-week window according to individual participants' needs.

Acupuncture therapy delivery was modified by the versions of the British Acupuncture Council's COVID-secure guideline current during the intervention period. The main points of this were to require:

- Cleaning of all surfaces touched by patients between appointments;
- Ventilation of the treatment room between appointments;
- The use of personal protective equipment including a type-IIR fluid-resistant face-mask and an impervious apron or front covering, plus a visor and gloves when in close proximity to patients' face, mouth and nose;
- The use of a screening tool as a permanent record of any COVID-19 symptoms for each patient at each appointment;
- Enhanced and more frequent hand-washing procedure;
- Practitioner lateral flow testing once or twice a week;
- Inclusion of COVID-19 transmission risk in a regularly-reviewed clinic risk assessment.

5.9.1.i The British Acupuncture Council

All Santé-AF acupuncturists were required to be members of the British Acupuncture Council (BAcC) (British Acupuncture Council, 2023). The BAcC is the only UK acupuncture membership organisation that holds a Professional Standards Authority Accredited Register for Health and Social Care (Professional Standards Authority, 2022). Organisations holding Accredited Registers require from their members a level of professional commitment including, for acupuncturists, a minimum BSc-level degree qualification, the maintenance of all necessary permits, licences and insurances, adherence to professional codes of practice and conduct, and the completion of a minimum number of professional development hours annually (British Acupuncture Council, 2023b).

5.9.2 Nutritional Therapy (NT)

Nutritional therapy (NT) is a new and developing discipline. Recent attempts to define the therapy have moved towards "personalised nutrition" as the preferred term (Tian et al., 2020), offering the

definition "a field that leverages human individuality to drive nutrition strategies that prevent, manage, and treat disease and optimize health" (Bush et al., 2020, p.5). Its goal is "to preserve or increase health using genetic, phenotypic, medical, nutritional, and other relevant information about individuals to deliver more specific healthy eating guidance and other nutritional products and services" (Ordovas et al., 2018, p.1). Santé-AF was designed before the term "personalised nutrition" became prevalent and therefore this thesis uses the term "nutritional therapy" throughout.

NT is based on biochemical and physiological principles of health and disease (Mozaffarian, Rosenberg and Uauy, 2018), but underpinned by a holistic perspective, i.e., "[the] understanding that human physiology functions as an orchestrated network of interconnected systems, rather than individual systems functioning autonomously and without effect on each other" (Nutritional Therapy Education Commission (NTEC), nd). The therapy is by nature multi-disciplinary, incorporating an understanding of genomics, epigenetics, functional medicine principles, behavioural science and systems biology to augment skills and knowledge in nutritional science and clinical practice (Bush et al., 2020; Konstantinidou, Ruiz and Ordovás, 2014).

The central feature of NT is the individualised dietary and lifestyle plan, resulting from a consultation in which information is collected from the patient on signs and symptoms potentially indicating factors such as compromised gut function, environmental factors, hormone and neurotransmitter regulation, detoxification, energy production and oxidative stress; patients may or may not have medical diagnoses of one or more health conditions. A resultant individualised strategy may include dietary advice, eating behavioural advice, supplementation, and lifestyle advice covering exercise, relaxation, sleep and social health; the strategy may be supported by privately commissioned functional and/or nutrigenomic testing dependent on the client's means (Ferguson et al., 2016). Through successive consultations, the NT supports the patient to adhere to the strategy, adjusting where necessary (Complementary and Natural Healthcare Council (CNHC), 2020). During consultations, the NT may practise one or more formal relationship management strategies such as Motivational Interviewing (Rollnick, Miller and Butler, 2022), or employ other skills such as coaching techniques (Weniger, 2021).

The complex nature of a personalised nutrition strategy means that mechanisms of action are multifarious and interactive; effects may be preventative or therapeutic, or both. Mechanisms of action may include, for example, the lowering of post-prandial blood glucose levels by means of a personalised diet integrating dietary habits, physical activity and gut microbiota (Zeevi et al., 2015); or the mediation of autoimmune symptoms via precise identification of the type of immune reaction, and the formulation of an appropriate individualised selective avoidance diet (Bush et al., 2020). For atrial fibrillation, "nodal points" affecting AF pathogenetic processes have been identified, including inflammation, oxidative stress, autoimmune mechanisms and visceral adiposity that may be

counteracted with personalised diet (Svinarich, 2021); broad strategies such as weight loss may also attenuate pathogenetic processes that may both reduce risk and attenuate symptoms (Tu et al., 2023). Other contributory mechanisms, including inflammation and atherosclerosis, are also amenable to nutritional interventions (Storz and Helle, 2019). Recent literature has begun to hypothesise that metabolites derived from gut microbiota may regulate cardiac substrate, and so may be leveraged in a therapeutic strategy (Gawałko et al., 2022; Tabata et al., 2021).

The scope of NT in the study was firstly defined to correspond with the core curriculum for nutritional therapy as set out by the CNHC (Complementary and Natural Healthcare Council (CNHC), 2020). This scope was largely defined by the study's available budget, which precluded the use of (i) functional or genomic testing, or (ii) supplementation. This meant that NTs on the study focused on dietary strategies and lifestyle advice.

Safe practice standards – particularly those relating to the recommendation of dietary strategies and lifestyle advice that may conflict with medication and specifically anticoagulant medication – were explicitly reiterated in the NTs' study manual (**Appendix A**, Practitioner documents section).

When explaining nutritional therapy or dietary principles, advising on self-care/lifestyle, or discussing underlying mechanisms or anticipated effects with participants, NTs were directed to follow their usual practice.

NT consultations were modified to avoid the risk of COVID-19 infection by being delivered online. Practitioners were asked to use their usual online video-calling software and routines for supporting participants to use this.

Participants were asked to contact the NT to arrange appointments at times to suit themselves. Practitioners were asked to regard as a desirable standard a treatment regime of once-monthly consultations during a twelve-week window, but were given flexibility to vary this according to individual participants' needs.

In keeping with the pragmatic nature of the study, NTs were advised that departures from the scope of practice were permitted if these could be justified in their clinical and professional judgement. The NTs' log book was used to capture any such departures.

5.9.2.i BANT, CNHC and NTEC

All Santé-AF nutritional therapists were required to be members of the British Association for Nutrition and Lifestyle Medicine (BANT), which is the UK's largest membership and self-regulatory body for nutritional therapists (British Association for Nutrition and Lifestyle Medicine, 2022).

BANT requires its members to be registered with the Complementary and Natural Healthcare Council (CNHC). The CNHC is a voluntary register of UK health practitioners constituting an

Accredited Register of the Professional Standards Authority for Health and Social Care (Professional Standards Authority, nd). CNHC members are required to be trained to National Occupational Standards and the CNHC's own core curriculum, to adhere to professional codes of practice and conduct, maintain full appropriate professional insurance, and complete a minimum number of professional development hours annually (Complementary and Natural Healthcare Council (CNHC), 2022).

NTs may only apply for CNHC registration (required by BANT membership) if they are graduates of a course accredited by the Nutritional Therapy Education Commission (NTEC) (Nutritional Therapy Education Commission (NTEC), nd). NTEC sets and updates the standards of training and education that meet the UK National Occupational Standards for nutritional therapy, and accredits NT training providers.

5.9.3 Usual Care

Usual care for Santé-AF comprised the care pathway as defined by the NICE guideline on AF (NG196) (National Institute for Health and Care Excellence, 2021), delivered via primary care practices in conjunction with hospital consultants and/or other healthcare professionals.

5.9.4 Safety of acupuncture and nutritional therapy

When carried out by appropriately trained practitioners, acupuncture and nutritional therapy present only minimal risks as defined by the sub-domains of the ICHOM Complications of Treatment domain (haemorrhagic stroke, major bleeding, serious adverse events post-intervention and side-effects) (Seligman et al., 2020).

Reviews of the safety of acupuncture compare favourably with those of current AF treatments. Witt et al. calculate that, on the basis of data from 2.2 million treatment sessions, the maximum risk of serious adverse effects of acupuncture treatment is 1:76,000 (2009). Adverse events associated with acupuncture are usually mild and self-correcting; the most frequent reactions are usually minor bruising around a needle site, insignificant bleeding on removal of needle, and transient dizziness (British Acupuncture Council, 2018). A 2012 review surveyed 468 reports of acupuncture-related adverse events to the UK's National Patient Safety Agency and concluded that 95% of adverse events were categorised as low or no harm (Wheway, Agbabiaka and Ernst, 2012). Of the remainder, 4% were classified as moderate harm, including loss of consciousness and "feeling unwell", and the study included one case of pneumothorax (where a needle punctured a lung). It should be noted that this data derives from treatments carried out by medical professionals in the UK's National Health Service (NHS), compared with traditional acupuncture practitioners; length of

discipline-specific training and level of qualification in acupuncture is higher amongst traditional acupuncture practitioners than in the NHS.

Nutritional therapy is a relatively new discipline, and as such its safety remains undocumented. Some safety data and investigations have been carried out for individual dietary interventions, such as low-carbohydrate diets (Oh, Gilani and Uppaluri, 2020); gluten-free diets (Saturni, Ferretti and Bacchetti, 2010); low FODMAP diets (Hill, Muir and Gibson, 2017); and low-fat diets (Dehghan et al., 2017). Most of these studies consider the risks of their target diet in a healthy population, which does not apply to an AF population with typical comorbidities. Additionally, the safety of personalised nutrition plans in which specific nutritional interventions are combined – the standard modus operandi of the nutritional therapist – is by nature difficult to investigate on a wide scale. Against this, nutritional therapy practitioners are trained to detect diet/medication and supplementation conflicts, and to take these into account in their advice (Nutritional Therapy Education Commission (NTEC), 2015).

5.9.5 Approach to treatment

As Santé-AF aimed to provide a high degree of generalisability to routine practice, practitioners were asked to deliver the interventions within their usual scope of practice, which was modified as described in the following sections. For both interventions, this included a component of self-care as a routine element of practice, following the World Health Organization's definition of the concept: "the ability of individuals, families and communities to promote health, prevent disease, maintain health, and to cope with illness and disability with or without the support of a health worker" (World Health Organization, 2022). Schedule of interventions

Participants assigned to the Acupuncture group were offered up to eight treatments; those assigned to the NT group were offered up to three consultations. Treatments/consultations were delivered at a frequency determined by the practitioner and participant.

In routine practice it is common for patients to interrupt a course of therapy by cancelling one or more appointments due to illness or other commitments, and greater fidelity to routine practice was anticipated if the study could allow for a level of such interruptions. Accordingly, participants were encouraged to complete their course of therapy within a specified window beginning at first appointment date and extending to 10 weeks for the Acupuncture group and 12 weeks for the NT group, to allow for unforeseen circumstances.

Data on attendance was collected using the practitioner log books (**Appendix A**, Practitioner documents section) and analysed to help answer objectives 3 (participant retention) and 4 (intervention acceptability).

5.9.6 Fees paid to practitioners

Practitioners were paid two types of fee: those covering the delivery of interventions and the extra administration required by the study (the CRN's Excess Treatment Costs); and those covering training and data collection (Research Costs). Fees were set in excess of the relevant market average for the following reasons:

- Recompense for study administration work, including completing each participant's log book; reading and signing contract documentation; registering with and invoicing the University of York; and submission of necessary permits and licenses for due diligence purposes;
- Recompense for the absence of premium chargeable for a first appointment (acupuncturists regularly charge a premium for a first appointment; NTs regularly offer packages in which the first-appointment premium is averaged over the package);
- As a financial incentive to help prevent attrition;
- [Acupuncturists only] Recompense for extra supplies and additional time for cleaning and ventilation between appointments required to comply with the BAcC COVID-19 guidelines.

Practitioners were also paid for non-attendance at appointments, for up to two appointments, reflecting standard cancellation policy in each profession (Vente, 2012; Healthie.com, n.d.).

All fees are shown in **Table 18**, along with a comparison with market averages where relevant (derived from an internet survey carried out in April 2019).

Table 18: Fees paid to practitioners

	Local market average in April 2019*	Paid by Santé-AF*
Fee per treatment, acupuncture	£50.00	£75.00
Fee per consultation, NT	£90.00	£114.00
Training workshops (2 x 3 hours)	–	£120.00
Exit interview (1.5 hours)	–	£75.00

* All fees averaged for all practitioners surveyed, across a course of appointments.

5.10 Methods to enhance participant retention

A number of methods were designed and incorporated into the study to enhance retention for both participants and practitioners (objective 3). These were not anticipated to violate the pragmatic

nature of the study, as they were aimed at encouraging study retention rather than treatment adherence (Chan et al., 2021).

5.10.1 Participant retention

Four methods were used to enhance retention of participants:

1. **Financial incentive:** The effectiveness of financial incentives is debated (Vellinga et al., 2020; Parkinson et al., 2019) and can even present disincentive in some types of study (Wenemark, Vernby and Norberg, 2010), but has been found effective in trials using questionnaires for follow-up evaluation (Gillies et al., 2021). In Santé-AF, participants who completed all assessments received a £10 retail voucher, intended as motivation to complete the study without presenting "undue inducement" (NHS Health Research Authority, 2014) or compromising the pragmatic nature of the study.
2. **Mitigating resentful demoralisation:** This is a theoretical issue in unblinded trials (Torgerson, Klaber-Moffett and Russell, 1996) in which participants withdraw or seek the intervention privately if not allocated to the study group of their choice. To mitigate this, the permission-to-approach pack, participant information pack and group placement letters all emphasised the societal value of taking part in research trials (Habets, van Delden and Bredenoord, 2014).
3. **Newsletter:** To mitigate attrition over the Christmas period, and to encourage a sense of study community and the societal value of participation, a Christmas-themed newsletter was written, designed and posted to all participants enrolled at 10th December 2021 (**Appendix A**, Miscellaneous section).
4. **Compliance prompting:** Participants were prompted by SMS messages (Keding et al., 2016) and phone calls from the researcher to return the symptom diary and CardioSTAT® ECG monitor (where applicable). In addition, participants received SMS reminders about the date and time of their baseline and follow-up assessments.

5.10.2 Practitioner retention

As practitioners were considered a type of participant in this feasibility study, and their retention was an important element in a future trial's feasibility, a range of methods was used to enhance practitioner retention (Parkinson et al., 2019):

1. **Contractual obligations:** Practitioners were contracted to the study via the University of York, and were required by the terms of their contract to deliver the agreed number of

interventions unless their clinical and professional judgement obviated this for a given participant (**Appendix A**, Practitioner documents section).

2. **Financial incentive for interventions delivered:** Practitioners were paid above the market rate for delivering the interventions.
3. **Community:** Research suggests that participation in peer support programmes improves healthcare practitioners' mental health and professionalism (Pereira, Radovic and Haykal, 2021). To support practitioners, a private, encrypted WhatsApp group was established for each practitioner group, alongside a second WhatsApp group for all practitioners. In addition, training sessions were undertaken in group settings (per therapy and study-wide); and an optional online peer supervision session was offered for practitioners in each therapy, towards the end of the intervention period. This was intended to support practitioners, build a sense of community and offer networking and professional development opportunities.
4. **Collaboration on journal articles:** Practitioners were offered the opportunity to collaborate on future case series articles to be published in practice-based professional journals. This was intended to support a sense of shared ownership of the study and its results, and to provide opportunities for professional development and contribution to the evidence base for the therapies.

5.11 Data collection

This section describes the design of the study's data collection instruments and the methods used to apply them, including the settings and locations of data collection.

As a mixed-methods study investigating two complex interventions, the Santé-AF study collected both qualitative and quantitative data to answer feasibility objectives.

Data collection and analysis is time-consuming for study staff, and may be burdensome for participants. Crowley and colleagues recently found that "a substantial amount [of data collection] is not related to trial outcomes" (2020, p.9). In investigating feasibility, Santé-AF attempted to justify all data collected in relation to one or more of the study objectives.

Data collected during the study fell into two categories:

1. **Data that directly addresses feasibility objectives.** This was analysed to answer the research question of this study, i.e., the feasibility of conducting a full-scale trial of acupuncture and nutritional therapy for symptoms and HRQoL in atrial fibrillation;

2. **Data that addresses the hypotheses of a future trial** regarding effectiveness of the two therapies, along with ancillary data required to carry out nested studies of participant responses to interventions, cohort characteristics, and treatment strategies used. This data was not analysed to answer feasibility objectives, but was still collected in order to investigate the feasibility of collecting this data from this population, using the specific methods outlined below.

Most of Santé-AF's data collection instruments and methods were designed for self-report by participants. The non-self-reported measures were the CardioSTAT® ambulatory ECG monitor, which was used to measure active AF; and anthropometric measurements (although in the feasibility study these were taken and reported by participants due to online working necessitated by COVID-19). The combination of both subjective and objective measures provides a degree of triangulation and meets good practice stipulations set out by international clinical organisations (Heros et al., 2023; Kluzek, Dean and Wartolowska, 2022; European Medicines Agency, 2014).

5.11.1 Study assessments

Study assessments were undertaken by participants only.

5.11.1.i Format of study assessments

Study assessments were originally designed to be conducted by the researcher at the study centre, with participants attending in person. Due to the COVID-19 pandemic, assessments were redesigned to be conducted online to minimise the risk of cross-infection. This decision (approved by the REC and HRA as Amendment 1 on 7th May 2021; **Appendix A**, Protocol and ethics section) necessitated the redesign of a number of data collection documents and methods (also approved), described in the sections below.

Study assessments were carried out online, with participants in a private space in their own home. The secure video-conferencing platform Whereby was used, as it was accessible via a standard internet browser and required no specialist software to be installed on participants' devices (Whereby, 2021). Links to meetings were emailed to participants using the email address given and consented for study use, shortly before the start of each assessment. Where participants did not have, or were not willing to use, a device with an internet browser installed, a study-dedicated internet-enabled tablet device (an Apple iPad) was offered. If the participant opted to use this, it was also included in the delivery and collection of assessment equipment. Where necessary, the researcher connected the iPad to the participant's home internet and tested the connection to ensure it was working.

COVID-19 infection prevention protocols were observed during delivery and collection. The researcher wore masks and non-latex gloves when present with participants, maintained the social distancing requirements current at the time, and did not enter any properties (where the iPad was connected to the participant's internet, this was carried out on the doorstep). All equipment was thoroughly cleaned with anti-viral wipes between uses, and the open, empty cases were ventilated in fresh air for a minimum of two hours between appointments. To allay anxiety, participants were informed of these measures during the screening call.

5.11.1.ii Timing and number of study assessments

Study assessments were carried out at baseline (i.e., before interventions began) and follow-up, a point defined as three months from date of allocation notification (for Usual Care) or end of treatment, whichever was later. For the Acupuncture and NT groups, the follow-up assessment was timed flexibly to account for the potentially extended durations of participants' individual course of therapy, but was anticipated to occur at approximately the same three-month point as for Usual Care. The delay caused by the COVID-19 pandemic precluded any longer follow-up period.

5.11.1.iii Scheduling of study assessments

Appointments were scheduled at a variety of times and dates to suit participants, including early mornings, evenings and weekends. The baseline assessment was scheduled during the screening call and confirmed to the participant subsequently by email. Participants were also sent two SMS reminders using the FireText SMS messaging service (FireText Communications Limited, 2019): one to confirm the appointment at the time of booking, and a second 72 hours in advance of the appointment. The follow-up assessment was scheduled by a phonecall made to the participant towards the anticipated end of their intervention period (Acupuncture and NT groups) or three months after the date of allocation notification (Usual Care).

Participants were informed of the likely duration of their study assessments, depending on their combination of subgroups, during the screening call. They were also informed that a case of equipment would be delivered to them by the researcher approximately one hour before the start of their assessment, and would be collected again approximately one hour after its end, and asked to take this into account when scheduling their study assessments. The researcher drove to the participant's home to deliver the equipment and back to the University of York to carry out the online assessment, returning to the participant's home to collect the equipment after the assessment.

5.11.1.iv Components of study assessments

Study assessments were carried out online, with the researcher in a quiet, private office to avoid breaches of confidentiality or participant dignity. Assessments comprised a number of elements, in the following order (see following sections for descriptions of instruments):

1. **Welcome and check,** including reading glasses, equipment, medications, clothing for warmth/dignity, device power levels/connection to power, protocol for loss of internet connection, participant comfort and any participant time restrictions.
2. **Completion of the questionnaire.** To complete the questionnaire, participants were invited to turn off their cameras if preferred, reminded to ask any questions that arose during questionnaire completion, and asked to spend as long as they wished answering the questions.
3. **Completion of interview (where applicable)**. Participants were informed that audio-recording would start, and offered the chance to turn off their camera if preferred.
4. **Self-fitting the CardioSTAT® ECG monitor** (where applicable). This followed a process designed and tested by Icentia during the successive UK lockdowns, in which the researcher had been trained. Participants were requested to stay on camera for supervisory purposes and guided through the necessary stages to securely fit the monitor and initiate recording. Once fitted, participants were informed about usage and safety restrictions. They were asked to remove the monitor after seven days (prompted by a timed SMS message) and return it to Icentia with their symptom diary (see below) in a secure pre-paid envelope supplied.
5. **Completing the symptom diary.** All participants were asked to complete a seven-day symptom diary, whether or not they were wearing a CardioSTAT®. During the assessment, all participants were asked to read through the blank diary and raise any questions. They were asked to stop completing the diary after seven days (prompted by a timed SMS message) and return it in a pre-paid envelope supplied.
6. **Medications Log.** All participants were requested to give details of their current medication regime on the day of the assessment, including dose level and frequency. The researcher recorded the details in the measurements and medications log (**Appendix C**), with a verbal check of each drug/dosage to ensure accuracy.
7. **Anthropometric data.** Because it was not feasible to supply participants with a stadiometer to measure height, participants were requested instead to give a self-report of their height along with details of when and how this was last measured. Following this, they were requested to remove clothing and guided to use the weighing scales to take two readings of their weight, a few minutes apart; these were reported to the researcher, who

entered them into the measurements and medications log, where they were automatically averaged. Participants were then guided to use the tape measure to measure their hips and waist circumference, and reported these to the researcher, who entered them in the log. Finally, participants were guided to take a blood pressure and pulse rate reading using an electronic monitor. The monitor was set to take three separate readings, 30 seconds apart, and to average these; the final reading was entered into the log.

8. **Final questionnaire section(s).** Participants were asked to return to the questionnaire and complete the section on their experience of the assessment, along with any subsequent sections.
9. **Thanks and close-out.** Participants were thanked for their time and requested to assemble all the equipment in its cases along with the completed questionnaire in its envelope for the researcher to collect. They were offered the opportunity to ask any questions about the assessment or the rest of the study, and reminded of the researcher's contact details in the case of any subsequent queries.
10. **Assessment timings.** During each assessment, the researcher kept a log of the time taken to complete each assessment, including each component (**Appendix C**). The log was also used to make any notes regarding characteristics of the assessment where these were thought likely to have affected data quality.

5.11.2 Questionnaires

Three questionnaires were completed by each participant during the study: the screening call questionnaire, the baseline questionnaire and the follow-up questionnaire. All collected a range of qualitative and quantitative data to provide composite data and a fuller response to various objectives (Meadows, 2022). All questionnaires were completed by participants in their own homes.

5.11.2.i Screening call questionnaire

The screening call questionnaire (**Appendix C**) was administered by the researcher, who asked all questions and recorded the answers during a phone call scheduled to suit the participant. This was carried out after full consent, but before randomisation.

The questionnaire was originally designed as a final-stage eligibility check using participant self-report to verify the eligibility items that were not available via the participant's medical records (**Table 16**), but for safety and study integrity reasons this questionnaire was redesigned to incorporate a full eligibility check. It also contained a number of questions to determine whether the participant was suitable for interview, and other questions to support study logistics (such as availability for appointments, confidence with technology, etc).

Quantitative and qualitative data from the screening call questionnaire was analysed to answer objectives 1 (participants' willingness to take part) and 2 (appropriateness of eligibility criteria).

5.11.2.ii Baseline and follow-up questionnaires

Two questionnaires were designed to capture feasibility and study data during the baseline and follow-up assessments. A brief outline of the content of each questionnaire is shown in **Table 19**, together with the objectives answered by each section. For the full questionnaires, see **Appendix C**.

Questionnaires were presented as an A4 booklet, of which the first page contained brief instructions for completion; the baseline questionnaire contained 21 subsequent pages, and the follow-up questionnaire 23 subsequent pages.

Two validated measures were incorporated into each questionnaire:

- the **EuroQoL EQ-5D-5L**, as a generic measure of health-related quality of life (HRQoL) (EuroQol Group, 2021). The EQ-5D family of questionnaires is widely used in economic evaluations of healthcare interventions (Wisløff et al., 2014), and has been used successfully in AF populations to demonstrate the relationship between population characteristics and HRQoL (Berg et al., 2010). This feasibility study incorporated a measure of HRQoL to test its acceptability and utility in this population. The EQ-5D-5L was chosen for its improved sensitivity and precision, and greater generalisability for longitudinal studies, over the EQ-5D-3L (Janssen, Bonsel and Luo, 2018).
- the **Atrial Fibrillation Effect on QualiTy of life (AFEQT)**, an 18-item disease-specific questionnaire which assesses the four domains of symptoms, daily activities, treatment concern and treatment satisfaction (Spertus et al., 2011). Incorporation of a disease-specific measure allows a greater degree of sensitivity to symptom change than the sole use of a generic instrument (Patrick and Reyo, 1989). Various patient-reported measures of individual AF severity exist; AFEQT was chosen for its reliability and sensitivity (Sale and Yu, 2022; Aliot et al., 2014; Rienstra et al., 2012).

Other sections of the baseline and follow-up questionnaires covered a range of feasibility objectives including acceptability of assessments and interventions (Sekhon, Cartwright and Francis, 2017), secondary outcome measures (general health and self-care/lifestyle), demographic and clinical data to investigate participant baseline characteristics including comorbidities, and health resources usage to inform future health economic analyses including changes in medication and hospital visits linked with AF and other conditions.

A variety of question styles was used, including closed answer-set, free text and ordinally scaled questions, and layout was clear and visually attractive to maximise response (Boynton and Greenhalgh, 2004).

Individual study data questions, and the questionnaires as a whole, were designed with input from the study's PPI panel. After feedback and minor adjustments, both questionnaires were piloted with a group of healthcare practitioner students, one of whom had a diagnosis of AF; further minor adjustments were made to layout and question phrasing.

Quantitative and qualitative data from the baseline and follow-up questionnaires was analysed to answer a range of objectives as shown in **Table 19** (see **5.2.3** for objectives).

Table 19: Outline of questionnaire content and related objectives

Q'aire	Section	Content overview	Objective addressed
Baseline	1	Demographic data, including COVID-19 data	Objective 1(d), 2(b), 3(f), 5(a), 5(b), 7(b)
Baseline	2	General health, including EQ-5D-5L	Objective 5(a), 5(b)
Baseline	3	AF symptoms (AFEQT) & changes to usual care	Objective 5(a), 5(b)
Baseline	4	Healthcare resources usage	Objective 5(a), 5(b)
Baseline	5	Self-care/lifestyle and its effect on AF symptoms	Objective 5(a), 5(b)
Baseline	6	Reasons for participating in study	Objective 1(a)
Baseline	7	Experience of study participation so far	Objective 7(a)
Baseline	8	Experience of baseline assessment	Objective 5(b)
Follow-up	1	Experience of therapy received	Objective 4(b), 5(a), 5(b)
Follow-up	2	General health, including EQ-5D-5L	Objective 5(a), 5(b)
Follow-up	3	AF symptoms (AFEQT) & changes to usual care	Objective 5(a), 5(b)
Follow-up	4	Healthcare resources usage	Objective 5(a), 5(b)
Follow-up	5	Self-care/lifestyle and effect on AF symptoms	Objective 5(a), 5(b)
Follow-up	6	Reasons for staying in study	Objective 3(e)
Follow-up	7	Experience of study participation/CardioSTAT®	Objective 6(b), 6(c), 7(a)
Follow-up	8	Experience of follow-up assessment	Objective 5(b), 5(c)
Follow-up	9	COVID-19 data	Objective 3(f), 4(c), 5(c), 7(b)
Follow-up	10	Overall participation acceptability, final comments	Objective 7(a)

5.11.2.iii Practitioner eligibility questionnaire

A questionnaire was designed to assess practitioner eligibility (**Appendix A**, Practitioner documents section), covering all elements within the practitioner eligibility criteria. For convenience, the questionnaire was administered online using Microsoft Forms; it consisted of 30 questions (acupuncturists) or 21 questions (nutritional therapists) plus one optional free-text question. A combination of question styles was used, including closed answer-set and free text questions.

Data from this questionnaire was analysed to answer objectives 1 (participants' willingness to take part) and 2 (appropriateness of eligibility criteria).

5.11.3 Interviews

In-depth semi-structured interviews were held during baseline and follow-up assessments to gather qualitative data from a subset of participants. All interviews were carried out online in participants' homes. The aim was to explore in greater depth some of the questions raised by the questionnaires, including participants' thoughts, feelings and beliefs about AF and study participation (DeJonckheere and Vaughn, 2019). Interviews took a broadly constructivist approach, understanding the exercise as socioculturally constructed by researcher and interviewee; the researcher interpreted the data during transcription and during the reflexive thematic analysis process (Braun and Clarke, 2021; Nascimento and Steinbruch, 2019), with a pragmatic focus on feasibility issues.

Interview topic guides (ITGs) were designed for the interviews. Questions were open-ended, broad and general to allow participants to convey and construct personal meanings (Creswell and Poth, 2018). The advice of the PPI panel was sought regarding whether AF-related topics and questions, together with their related prompts and probes, were relevant and ethical.

Baseline ITGs (**Appendix C**) were identical for all participants, and covered topics relating to diagnosis, NHS treatment, living with AF and its effect on self-care/lifestyle; and topics relating to participation, including the effect of the COVID-19 pandemic on participation, and study/assessment experience.

End-of-treatment ITGs (**Appendix C**) differed according to participant group. Acupuncture and Nutritional Therapy ITGs included participants' experience of their therapy, while the Usual Care ITG included participants' experience of their usual care during the previous three months. All groups' ITG topics included experience of self-care/lifestyle advice during the study period, experience of participation and experience of the baseline/follow-up assessments.

In interview, the ITGs were applied flexibly – while all areas were explored, the nature of the participant's individual experience was allowed to direct those areas to which more focus was given. Interviews were audio-recorded; participants were offered the opportunity to turn off their cameras, but if cameras were left on, video was recorded in addition. Participants were made aware of this.

Data from the interviews was analysed to answer objectives 1 (participants' willingness to take part), 3 (participant retention), 4 (intervention acceptability), 5 (acceptability of study assessments) and 7 (experience of study participation).

5.11.3.i Interviews for practitioners

Individual semi-structured interviews were held with all practitioners at end-of-treatment (EOT) to explore their thoughts, feelings and beliefs about a range of topics relating to their participation in the study. Four of the six interviews were held online; for the remaining two, the researcher travelled to the practitioners' homes. Interviews held online were video-recorded; all interviews were audio-recorded.

Two interview topic guides (ITGs) were devised, one for each therapy (**Appendix A**, Practitioner documents section). Topics included motivation, study admin, financial aspects of the study, logistical issues of participation, support offered, and working with study participants. Acupuncturists were asked about their feelings regarding adherence to the COVID-19 code of safe practice required by their professional body; nutritional therapists were asked about their feelings regarding working entirely online due to the pandemic.

Data from the practitioner interviews was analysed to answer objectives 1 (participants' willingness to take part) and 7 (experience of study participation).

5.11.3.ii Interviews for PICs

PICs were asked to attend a short interview (15 minutes or less) to evaluate their experience of the participant identification process. All interviews were carried out online while staff were on practice premises.

5.11.4 Other data collection instruments and methods

5.11.4.i PIC search and screening log

A log was designed using Microsoft Excel to capture details of the search/screening process at each PIC (**Appendix A**, Participant identification and randomisation section). The process required a member of staff to search the database for patients meeting the first two inclusion criteria, and a medically qualified person to screen the results against two further inclusion criteria (3 and 12) and then against exclusion criteria 1–9 and 11-13. To help answer objective 2(a), PICs were asked to log *all* reasons for exclusion for a given patient, rather than stopping at the first exclusion criterion. The log, which was pseudonymised and completed on GP practice premises, generated a count of patients judged eligible by criteria derived from medical records.

Data from the PIC search and screening log was analysed to answer objective 2 (appropriateness of eligibility criteria).

5.11.4.ii Permission-to-approach and consent forms

Some data was collected via the permission-to-approach forms (**Appendix C**) returned to the researcher, including identity and contact details for patients who consented to receive more information about the study. Non-consenting patients were invited to give optional, brief information about their reasons for declining. Similarly, on the full informed consent form sent to patients who consented to receive more information about the study (**Appendix C**), non-participating patients were invited to give more information about their reasons for declining.

Data from both forms was analysed to help answer objective 1 (participants' willingness to take part).

5.11.4.iii SMS poll

A poll of participants was carried out by SMS to determine:

1. Satisfaction levels for group allocation;
2. Treatment expectation for the allocated intervention, relating to AF symptoms.

SMS messages were sent manually to each participant two days after receipt of postal notification of allocation, using the mobile phone number given and consented for use during the study by each participant. Messages were sent via the FireText secure SMS messaging system which is approved by NHS Digital for healthcare communications with patients (FireText Communications Limited, 2019). The first message requested a rating for group allocation satisfaction on a scale of 1-10, where higher numbers = greater satisfaction. The second message asked for treatment expectation using three nominal categories (get worse, stay about the same, improve).

Data from the SMS poll was analysed to answer objectives 4 (intervention acceptability) and 5 (acceptability of study assessments).

5.11.4.iv Symptom diary

A symptom diary (**Appendix C**) was designed to capture data on AF episodes (date, time, symptoms, duration, activity levels at onset and participants' assessment of severity) over a seven-day period starting at each assessment. All participants were requested to complete the diary, even if they were assigned to wear a CardioSTAT® ECG monitor in addition. The diary was presented as an eight-page A5 booklet which participants were asked to keep close at hand to record details of each episode as soon as possible after onset/offset. Participants were given a stamped addressed envelope for the return of the symptom diary after the seven-day period had elapsed.

Data from the symptom diary was analysed to answer objectives 5 (acceptability of study assessments) and 6 (utility of CardioSTAT® monitor).

5.11.4.v Anthropometric measuring equipment

Participants were supplied with an electronic weighing scale (Salter Limited, 2023), a tape measure (Seca UK, 2023) and a digital blood pressure monitor (Omron UK, 2023) and guided by the researcher during the study assessments to follow standard processes to take these measurements. All instruments were checked and recalibrated before the start of the baseline assessments, and again before the start of follow-up assessments, to minimise the possibility of measurement error. Data was recorded by the researcher in the measurements and medications log (**Appendix C**).

Anthropometric data was analysed to answer objective 5 (acceptability of study assessments).

5.11.4.vi Medications data

Data on participants' medications, including dose, was collected during the baseline and follow-up assessments to understand any changes in relation to possible polypharmacy. Data was recorded by the researcher in the measurements and medications log (**Appendix C**).

Medications data was analysed to answer objective 5 (acceptability of study assessments).

5.11.4.vii CardioSTAT® ECG monitor

A third of participants was randomly assigned to wear a CardioSTAT® two-lead ambulatory ECG monitor at baseline and follow-up assessments (**Appendix C**). The model used in Santé-AF captured active AF over a seven-day period. Participants were guided to self-fit the monitors during the assessments and provided with a postage-paid envelope that could be dropped off at a local Post Office for return direct to the manufacturer, Icentia Ltd. Specialist data analysis was carried out by Icentia, providing a pseudonymised report to the researcher, the Santé-AF consultant cardiologist and the participant's GP. Participants assigned to wear a CardioSTAT® were also asked to complete a symptom diary, as per all other participants.

Data from the CardioSTAT® monitors was analysed to answer objectives 5 (acceptability of study assessments) and 6 (utility of CardioSTAT® monitor).

5.11.4.viii Practitioner log books

As Santé-AF studied two complex interventions, data was collected from practitioners to inform an analysis of the scope of practice in a future trial. Practitioner log books were designed to capture details of the individualised treatment approaches and components of interventions used for each participant, at each appointment (**Appendix A**, Practitioner documents section).

In the log book, acupuncturists were also required to complete a checklist of COVID-19 precautions set out by the British Acupuncture Council, and to provide a rationale if any precautions were not taken.

An end-of-treatment summary for both interventions also required details of whether and why the course of treatment had ended early; the central principles of the therapeutic approach used; the practitioner's observations regarding whether and how COVID-19 had affected the patient or their treatment; any comments on outcome, adherence to self-care/lifestyle advice; and any protocol violations.

The log book was presented as an A4 booklet of 20 pages (Acupuncture) or 12 pages (NT). An editable PDF version of both therapies' log books was also available for download from the secure area of the study website (**www.sante-af.org**).

Data from the log books was analysed to answer objectives 4 (intervention acceptability) and 5 (acceptability of study assessments).

5.11.4.ix Observational data from study progress

Observational data on the study's progress was used to help answer feasibility objectives. These included numbers of participants randomised (objective 1), retained at various stages (objective 3), and excluded by each exclusion criterion (objective 2); and the completeness of data returned by participants (objective 5).

5.12 Data analysis methods

Santé-AF used mixed methods (Creswell and Creswell, 2018; Morse, 1991) to enable a full understanding of both *whether* specific elements of a future trial's design are, or are not, feasible; and *why* this may be so, giving a richer understanding of feasibility to inform the recommendation of changes for a future trial (Aschbrenner et al., 2022).

5.12.1 Quantitative data analysis

The overarching intent of quantitative data analysis was to yield an understanding of *whether* a given domain of the future trial design was feasible; quantitative analysis focused specifically on the progression criteria. All analyses used complete cases only. Some analyses were done on a per-group basis where appropriate.

In keeping with advised methods for pilot and feasibility studies (Teresi et al., 2023; Lee et al., 2014), this study used descriptive statistics including means and standard deviations, and count

data including percentages, to analyse and report quantitative feasibility data. This included an overall judgement of feasibility for each domain and at study level.

5.12.2 Qualitative data analysis

The overarching purpose of qualitative data analysis in Santé-AF was to yield an understanding of *why* a given domain of the future trial design is feasible or not (Aschbrenner et al., 2022; Busetto, Wick and Gumbinger, 2020).

Reflexive thematic analysis (RTA) (Braun and Clarke, 2019) was used throughout Santé-AF, with the intent of "identifying patterns ["themes"] across qualitative datasets" (Braun et al., 2019, p.843) to inform feasibility findings. RTA was an appropriate choice of qualitative analysis method for this study, as its approach aligns with the social constructivist, pragmatic approach of the study (Byrne, 2022).

The explicitly reflexive component of this method also mitigates an element of researcher positionality, that web of "philosophical sensibility and theoretical assumptions [that] are consistently, coherently and transparently enacted throughout the analytic process and reporting of the research" (Braun and Clarke, 2019, p.594); reflexivity was a particularly useful element of the data analysis method in view of the fact that the researcher was also a practitioner (of acupuncture), although not delivering interventions in the study. RTA therefore was chosen to mitigate some of the ways in which the researcher-practitioner perspective may have shaped interpretation and results, by declaring them and making them more transparent (Berger, 2015; Guillemin and Gillam, 2004). In fact, the RTA approach positively embraces researcher positionality as an analytic resource: "Themes are creative and interpretive *stories* about the data, produced at the intersection of the researcher's theoretical assumptions, their analytic resources and skill, and the data themselves" (Braun and Clarke, 2019, p.594).

A researcher positionality statement was written (**Appendix A**, Miscellaneous section) and regularly revisited to inform entries in a reflexive journal that was kept throughout the data analysis process (Wilson, Janes and Williams, 2022). The journal used extended coding memos to record awareness of bias and reasons for analytical interpretations (Alvesson, Hardy and Harley, 2008), particularly where these involved interpretation that evoked personal or professional biases (Daniels, Gillen and Casson, 2021; Doyle, 2019). Where data meaning was unclear, or where interpretation was thought to be particularly vulnerable to the researcher's positionality, the perspectives of the study's practitioners (including those in the treatment group to which the participants in question were *not* allocated) were sought in a spirit of co-interpretation.

The RTA process uses a six-step process beginning with data familiarisation, progressing through semantic and latent code generation, grouping codes into candidate themes, refining themes over

two further stages and finally writing up (Byrne, 2022; Braun and Clarke, 2021). To help organise material, NVivo qualitative data analysis software was used (Lumivero, 2023). Results of RTA analyses were reported independently at domain level, or in mixed methods synthesis at objective level. Analytic themes were focused on feasibility rather than the primary investigation of participants' thoughts, beliefs and opinions: for instance, in assessing the acceptability of assessments, themes were focused around aspects of the assessments such as the questionnaires, or online working, rather than being structured by participants' thoughts, beliefs and opinions. This practical focus on feasibility borrowed from the principles of framework analysis (Srivastava and Thomson, 2009), but retained an inductive approach that allowed thoughts, beliefs and opinions to be heard and included in the feasibility assessments and recommendations (Braun et al., 2019).

5.12.3 Mixed methods synthesis

Santé-AF applied mixed methods synthesis at individual objective and overall study levels. Appropriate quantitative and qualitative data sources have been identified; integrative analyses were planned to determine feasibility; and "meta-inferences" and implications for a future trial were drawn from the integrated data (Aschbrenner et al., 2022). The study used a convergent design which collected qualitative data simultaneously with quantitative data, then analysed and merged the results (Aschbrenner et al., 2022; Creswell, 2015). This produced a composite, more nuanced picture of feasibility (Meadows, 2022), enabling recommendations to be made to increase feasibility of a future large-scale trial.

Integration of quantitative with qualitative data focused on an exploration of the extent to which qualitative and quantitative results were consonant or dissonant with each other. To this end, a significant overlap was planned between quantitative questions in questionnaires and qualitative questions in interviews (Tariq and Woodman, 2013). To integrate both types of data, joint displays were used (Creswell and Plano Clark, 2018; Guetterman, Fetters and Creswell, 2015); the use of tables or figures to synthesise quantitative and qualitative data provides a concise but illustrative means of exploring both consonant and dissonant findings, with a view to enhancing an understanding of feasibility (Aschbrenner et al., 2022; Tonkin-Crine et al., 2015).

5.13 Progression criteria

The focused methodological review carried out to inform the design of Santé-AF found that progression criteria should be mapped to feasibility objectives; should be justified; should consider quantitative and qualitative interpretations of feasibility; and should be considered as a collective

whole rather than in isolation (Mellor et al., 2023, 2022, 2021; Mbuagbaw et al., 2019; Young et al., 2019; Avery et al., 2017). Santé-AF did not incorporate any qualitative progression criteria, as feasibility objectives were designed to be measured by quantitative progression criteria (Mbuagbaw et al., 2019); however, most were designed to be co-informed by qualitative analysis (Baldeh et al., 2020). Following Mellor et al.'s recommendations, progression criteria were mapped to feasibility objectives, and intended as guidelines rather than absolute rules (Mellor et al., 2023).

Descriptive statistics were used to assess whether quantitative progression thresholds were met (Hallingberg et al., 2018). Reflexive thematic analysis provided qualitative assessment informing the quantitatively-measured outcomes. For those objectives that did not meet the progression threshold, the ADePT process was used to determine whether intervention, trial design or context should be changed to increase feasibility, using qualitative data to understand what could be changed and how (Bugge et al., 2013).

5.13.1 Setting progression thresholds

To set progression thresholds, a short survey was conducted of 15 trials or pilots/feasibility studies of broadly comparable interventions for cardiac conditions and/or AF comorbidities. Information on the studies, and the data extracted, can be found in **Appendix A**, Miscellaneous section.

Thresholds for each objective were set as shown in **Table 20** (overleaf): this shows the objective, the domain measured, the feasibility threshold and rationale. Not all the feasibility objectives investigated by Santé-AF were found in comparable studies – for instance, overall acceptability of study participation and levels of allocation satisfaction were not reported in any of the sampled trials.

Table 20: Progression thresholds for each objective, with source

#	Objective	Measurement	Feasibility threshold	Rationale
1	Participants' willingness to take part	Percentage of eligible participants randomised	⩾ 90%	Survey of recent similar trials*
2	Appropriateness of eligibility criteria	Demographic and clinical characteristics of randomised participants	⩽ 20% difference	Comparison with recent AF cohorts**
		Percentage of identified participants eligible	⩾ 60%	Survey of recent similar trials*
3	Participant retention	Percentage of randomised participants retained	⩾ 80%	Survey of recent similar trials*
4	Acceptability of interventions	Participant report of allocation satisfaction	⩾ 75% reporting 7-10 on 10-point scale (10 = most satisfied)	Jobst, Leppla and Köberich, 2020
		Participant report of acceptability of intervention	⩾ 75% reporting 1-3 on 7-point scale (1 = most acceptable)	Jobst, Leppla and Köberich, 2020
5	Acceptability of participant assessments	Completeness of questionnaires and assessment data collected	⩾ 80% of all data collected	Jobst, Leppla and Köberich, 2020
		Participant report of acceptability of assessment	⩾ 90% reporting 1-3 on 7-point scale (1 = most acceptable)	Jobst, Leppla and Köberich, 2020
6	Utility of CardioSTAT® ECG monitor	Number of AF episodes recorded by ECGs not noted on AF symptom diary	≤ 1	no precedents found
		Participant report of influence of monitor on decision to participate in study	⩾ 50% reporting 1-2 on 5-point scale (1 = most influential)	no precedents found
7	Participant experience of study participation	Participant report of acceptability of study participation	⩾ 75% reporting 1-3 on 7-point scale (1 = most acceptable)	no precedents found

* for this survey, see **Appendix A**, Miscellaneous section: Objectives survey and feasibility thresholds

5.14 Changes to methods after study start

As a feasibility study, Santé-AF was exploratory in nature. Several adjustments were made after the start of the study to explore some aspects of feasibility not included in the original objectives (Eldridge et al., 2016a). These are described below.

5.14.1 Analysis plans

Calculations of group means on the primary outcome measure were added to the study on the advice of academic supervisors. Progression criteria were not devised or applied.

A number of exploratory analyses were carried out using existing data, to inform fuller understandings of feasibility. These are clearly marked as exploratory analyses in the following chapter.

5.14.2 COVID-19

Due to the COVID-19 pandemic, some aspects of the original protocol's methods were changed to ensure participant and practitioner safety, and can be considered "important modifications" according to the definitions proposed by Orkin et al. in the CONSERVE-CONSORT 2021 reporting guideline (Orkin et al., 2021). All are reported in **5.3.1.i**.

The original study protocol was modified to include an objective investigating the feasibility of all objectives during the COVID-19 pandemic (**Appendix A**, Protocol and ethics section). However, unless a future trial were to take place under similar conditions, this objective was judged not to be useful and was therefore removed as a separate objective; progression criteria were not applied. Where the COVID-19 pandemic influenced feasibility, this was included in data analysis and the results reported in **Chapter 6**.

5.14.3 Safety of interventions

It was not part of the original protocol's methods to investigate the safety of the interventions in Santé-AF: the small sample size of the study is unsuited to the investigation of effects, and it was thought that this study's systematic review (**Chapter 3**) would be better able to respond to a research question focused on intervention safety. However, the review revealed very little evidence for either acupuncture or nutritional therapy in the treatment of AF, and therefore their safety could not be investigated using secondary methods.

In this light, even the small sample size of Santé-AF was thought to contribute valuable safety data for both therapies. An analysis of safety for both interventions during the study was therefore carried out using data gathered from practitioner log books and general study communications.

5.14.4 Participant identification process

To explore questions of whether the participant identification process was fit for purpose and likely to have generated robust data, PICs were invited to an interview on their experience of the participant identification process. Data was collated to evaluate any areas for improvement in a future trial.

5.14.5 Screening call questionnaire

The screening call questionnaire (completed by the researcher with data given by the participant) was redesigned to incorporate a full eligibility check following search errors by one PIC that resulted in participant information packs being sent to a number of ineligible patients (**5.7.1.iii**).

5.14.6 Practitioner peer supervision groups and communications

Two peer supervision meetings were held (one for each therapy) during the intervention period. WhatsApp groups were also used for practitioner communications.

5.14.7 Change of focus for objective 1

In the study protocol, objective 1 originally focused on participants' willingness to be randomised. This was changed to the willingness of participants to take part, in order to examine broader issues regarding participation. Within this, data was also collected and analysed regarding participants' willingness to be randomised.

5.14.8 Pragmatism in Santé-AF

For the purposes of pilot/feasibility studies, Chan et al. (2021) modified the pragmatic-explanatory continuum indicator (PRECIS-2) tool, which indicates the extent to which all major domains of a trial can be considered pragmatic or explanatory. Unfortunately this modified tool was published after Santé-AF had begun to recruit, and the study design could not be changed. The domains in the modified tool were considered in case they suggested any additional aspects of feasibility that could be answered using data that was already planned to be collected. One feasibility domain was added: Intervention fidelity (objective 7e); and one exploratory analysis was conducted: Research ethics. Both used existing data collected during the study. They are reported in **Chapter 6** and discussed in **Chapter 7**.

5.15 General study information

5.15.1 Trial registration

The study was registered on the ISRCTN trials registry (ISRCTN13671984) on 4th June 2020.

5.15.2 Study protocol

Following the recommendation of Moore et al. (2011), a protocol was written to guide the design and implementation of Santé-AF. See **Appendix A**, Protocol and ethics section.

5.15.3 Study funding

Funding for the study was provided by a research grant of £10,000 from the British Acupuncture Council (BAcC), a non-commercial partner of the Association of Medical Research Charities (National Institute for Health and Care Research, 2023). BAcC funding rendered Santé-AF eligible for portfolio-adopted study status with the Yorkshire & Humber branch of the Clinical Research Network (CRN). The CRN supplied:

- Assistance with the recruitment of Participant Identification Centres (PICs);
- Service Support Costs (SSCs) covering some of the PICs' activities;
- Excess Treatment Costs (ETCs) covering fees for practitioners delivering the interventions.

For further details of the CRN funding, see the Schedule of Events Cost Attribution Template (SoECAT); for details of how the BAcC research grant was allocated, see the Santé-AF study outline costings (**Appendix A**, Funding and costings section).

The researcher was also supported by funding from the Northern College of Acupuncture (York, UK), amounting to £9,000 in payment of doctoral programme tuition fees.

The funders determined the therapies included in the study: the BAcC research grant was awarded for an experimental investigation of acupuncture, while the NCA advocated the inclusion of a nutritional therapy group in the study.

Neither funder had any influence on the design, conduct, reporting or dissemination of the study.

5.15.4 Ethical approval

Favourable ethical opinion was given by the NHS HRA London Surrey REC along with HRA approval on 3 November 2020 (REC reference 20/LO/0598).

5.15.5 Study personnel

For the purposes of GCP governance, the Chief Investigator was one of the researcher's academic supervisors, Dr Jude Watson. The Principal Investigator was the researcher.

5.15.6 Trial indemnity

Indemnity was provided by the University of York; the NHS; and practitioners' own professional insurance.

5.15.7 Data management

To reduce data-related risk and demonstrate compliance with the General Data Protection Regulation (GDPR), this study used appropriate pseudonymisation, data minimisation, limitation and protection of storage, access restrictions and organisational measures.

The University of York processes personal data for research purposes under Article 6(1)(e) of the GDPR. Processing is necessary for the performance of a task carried out in the public interest (Health Research Authority, 2018).

The study's legal basis for processing under the GDPR is Condition (j) (scientific research) in Article 9 (2) of the General Data Protection Regulations (European Parliament and Council of the European Union, 2018).

For the full data management plan for this study, including formats, storage, duration of storage and access, see Table 9 in the study protocol (**Appendix A**, Protocol and ethics section).

6 Results

This chapter presents the results of the feasibility study. This chapter is structured around the feasibility objectives together with a number of supplementary exploratory analyses. Progression criteria are applied to each objective. General findings are also presented (i.e., those not specific to the feasibility objectives but of interest to a future trial) and the chapter concludes by making a quantitative determination of overall feasibility.

Study ID numbers for participants are given here as PIC number followed by a three-digit unique identifier, followed by study group (2/761/A, 4/142/NT, 1/884/UC, etc). Note that the study group identification was appended during the data analysis stage, and did not affect allocation concealment for participants. ID numbers for practitioners are given as P#/therapy (P1/A, P4/NT, etc).

Figures are reported to one decimal place unless differences are small enough to require more.

Participants' progress is set out in the CONSORT flow diagram (Eldridge et al., 2016a) shown in **Figure 7** (overleaf).

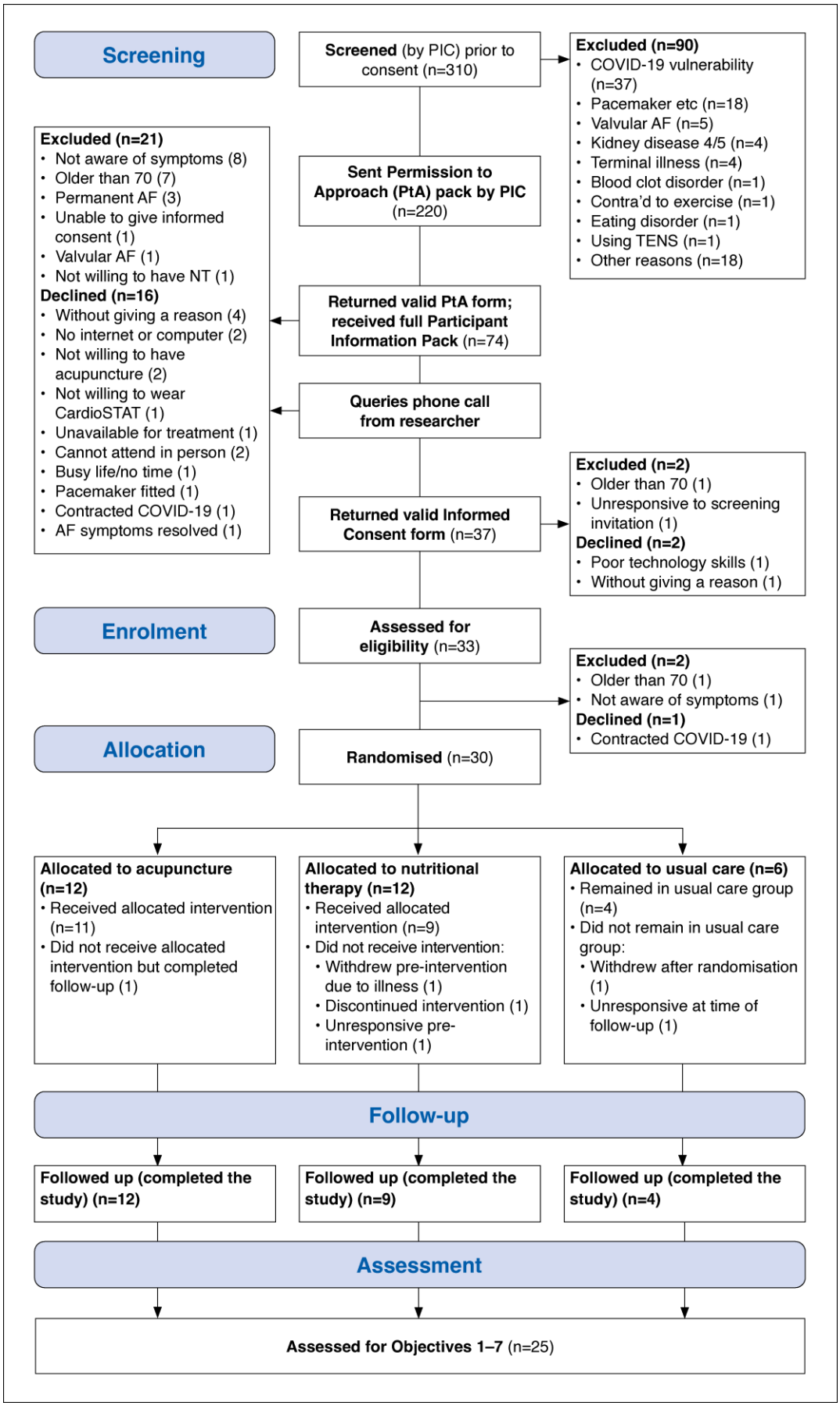

Figure 7: CONSORT flow diagram

Table 21 shows the baseline characteristics of participants, per group.

The participants were 100% ethnically white, aged between 56-61, with n=22 (75.9%) male to n=7 (24.1%) female. The sample overall demonstrates a range of educational attainment level from no qualifications (n=2 or 6.9%) to postgraduate higher education qualifications (n=5 or 17.2%), with the most frequent highest attainment level being further education (n=12, or 41.4% of the total participant group). Participants also demonstrate a range of home ownership status from owner-occupier without mortgage (n=16 or 55.2%) to renting from the local council or housing association (n=2 or 6.9%).

There are some notable baseline imbalances between groups, including a lower mean age in the UC group; an imbalance in sex within the NT and UC groups; duration of AF diagnosis, alcohol intake and average AFEQT score between UC and the intervention groups; and the average number of comorbidities between the UC and intervention groups.

Table 21: Baseline characteristics of participants, per group

	Acupuncture (n=12)	Nutritional Therapy (n=11)	Usual Care (n=6)
Age	61.1±4.9	61±5.5	56.3±8.9
Sex			
Male	7 (24.1%)	10 (34.5%)	5 (17.2%)
Female	5 (17.2%)	1 (3.4%)	1 (3.4%)
Ethnicity			
White	12 (41.4%)	11 (37.9%)	6 (20.7%)
Highest educational attainment			
No qualifications	–	2 (6.9%)	–
CSEs, O-levels, GCSEs	2 (6.9%)	–	–
Further education	4 (13.8%)	4 (13.8%)	4 (13.8%)
Higher education undergraduate	3 (10.3%)	1 (3.4%)	–
Higher education postgraduate	–	3 (10.3%)	2 (6.9%)
Vocational qualifications	3 (10.3%)	1 (3.4%)	–
Other qualifications	–	–	–
Home ownership status			
Owner-occupier, without mortgage	7 (24.1%)	7 (24.1%)	2 (6.9%)
Owner-occupier, with mortgage	4 (13.8%)	2 (6.9%)	4 (13.8%)
Renting with council or housing association	–	2 (6.9%)	–
Renting privately	1 (3.4%)	–	–
Residential care or nursing home	–	–	–
Average duration of AF, months	41.3±23.9	38.8±17.5	28.3±18.8
Average AFEQT score (higher = better)	71.1±20.4	76.2±13.9	63.4±32.3
BMI	31.3±6.1	28.4±5.1	31.8±3.7
Waist-hip ratio			
Male	0.97±0.03	1.00±0.06	1.02±0.04
Female	0.89±0.04	0.92*	0.90*

Blood pressure, mmHg			
Systolic	142.8±23.4	146.4±20.8	144±18.5
Diastolic	92.8±6.9	94.9±12.4	91.3±8.3
Comorbidities			
Average number comorbidities per participant	1.1±1.4	1.3±1.4	1.8±2.3
Anaemia	–	–	1 (3.4%)
Angina	–	–	1 (3.4%)
Cardiomyopathy	–	–	–
COPD	–	–	1 (3.4%)
Coronary heart disease	–	1 (3.4%)	–
Diabetes	1 (3.4%)	3 (10.3%)	–
Enlarged prostate	1 (3.4%)	–	–
GORD	–	–	1 (3.4%)
Heart failure	–	–	–
Hyperlipidaemia	1 (3.4%)	2 (6.9%)	–
Hypertension	3 (10.3%)	5 (17.2%)	3 (10.3%)
Hyperthyroid/Graves	–	–	–
Myocardial infarction	1 (3.4%)	–	–
Obesity	1 (3.4%)	1 (3.4%)	–
Parkinson's Disease	1 (3.4%)	–	–
Peripheral vascular disease	–	–	–
Prior CVA or TIA	–	2 (6.9%)	–
Sarcoidosis	–	1 (3.4%)	–
Sleep apnoea	2 (6.9%)	–	2 (6.9%)
Tinnitus	–	–	1 (3.4%)
Smoking			
Current smoker	0	0	0
Ever smoker	9 (31.0%)	7 (24.1%)	4 (13.8%)
Time since cessation, mo	287.7±192.6	287.3±195.5	277.6±181.4
Units alcohol/week	23.9±24.9	22.6±17.1	14.0±16.4
Medication			
Average number of medications per participant	3.8±2.3	3.7±2.0	3.8±1.9
5-alpha reductase inhibitor	2 (6.9%)	–	–
ACE inhibitor	2 (6.9%)	3 (10.3%)	1 (3.4%)
Alpha blocker	1 (3.4%)	2 (6.9%)	–
Analgesic	1 (3.4%)	–	–
Antacid	–	1 (3.4%)	–
Anti-arrhythmic	–	–	1 (3.4%)
Anti-hypertensive	–	–	1 (3.4%)
Antihistamine	1 (3.4%)	–	–
Anti-hyperglycaemic	–	2 (6.9%)	–
Antimuscarinic	–	1 (3.4%)	–
ARB/ARNI	1 (3.4%)	1 (3.4%)	2 (6.9%)
Beta-3 adrenergic agonist	1 (3.4%)	–	–
Beta-blocker	11 (37.9%)	5 (17.2%)	3 (10.3%)
Bronchodilator	–	–	3 (10.3%)
Calcium channel blocker	4 (13.8%)	2 (6.9%)	2 (6.9%)
Carbonic anhydrase inhibitor	–	1 (3.4%)	–

Corticosteroid	–	1 (3.4%)	1 (3.4%)
Diuretic	1 (3.4%)	1 (3.4%)	1 (3.4%)
Hormone replacement therapy	1 (3.4%)	–	1 (3.4%)
Insulin	–	1 (3.4%)	–
Nitrate	1 (3.4%)	–	1 (3.4%)
NOAC	7 (24.1%)	8 (27.6%)	5 (17.2%)
Other anticoagulant	1 (3.4%)	1 (3.4%)	–
Proton pump inhibitor	3 (10.3%)	3 (10.3%)	1 (3.4%)
SSRI	1 (3.4%)	–	–
Statin	5 (17.2%)	7 (24.1%)	–
Thyroid hormone	1 (3.4%)	–	–
Xanthine oxidase inhibitor	–	1 (3.4%)	–

Figures are means ± standard deviation or count data (with percentage of total N in trial)

* Figure applies to the single female participant in this group (therefore figure is not a mean, and no standard deviation is given)

ARB/ARNI angiotensin receptor blocker/angiotensin receptor/neprilysin inhibitor; **ACE** angiotensin-converting enzyme; **COPD** = chronic obstructive pulmonary disease; **CVA** cardiovascular accident; **GORD** gastro-oesophageal reflux disease; **mo** months; **NOAC** novel oral anticoagulant; **SSRI** selective serotonin reuptake inhibitor; **TIA** transient ischaemic attack

6.1 Objective 1: Willingness to take part

This objective focused on recruitment to the study, and was divided into eight domains, of which two focus on practitioners and two on Participant Identification Centres (PICs). The recruitment period is defined as the time from the first permission-to-approach form received to the final consent form received (25th October 2021 to 21st January 2022, a period of 88 days).

6.1.1 Objective 1a: Participants' reasons for participation

This domain was answered using both qualitative and quantitative data gathered from the baseline questionnaire and interviews.

6.1.1.i Quantitative analysis of reasons for participating

The baseline questionnaire asked participants to nominate all that applied from a pre-defined list of reasons for participation, together with a free-text "other reasons" box. Of these, they were then asked to nominate the most important reason. Results are shown in **Table 22** (overleaf).

Table 22: Participants' reasons for participating, and most important reasons

	n (%) of 29 participants citing this reason	n (%) of 29 participants citing this as most important reason
Curious about acupuncture	25 (86.2)	6 (20.7)
Wanted to help others with AF by contributing to knowledge base	23 (79.3)	6 (20.7)
Curious about medical research	25 (86.2)	4 (13.8)
Curious about complementary therapies in general	13 (44.8)	4 (13.8)
Wanted chance to have AF monitored by a CardioSTAT® ECG monitor	7 (24.1)	3 (10.3)
Wanted to have some free treatment that might help	9 (31.0)	2 (6.9)
Curious about nutritional therapy	19 (65.5)	1 (3.4)
Other:		
Wanted an alternative to medication	2 (6.9)	1 (3.4)
Wanted acupuncture, hoping it would cure AF	1 (3.4)	1 (3.4)
Dissatisfied with NHS treatment	9 (31)	0
Wanted more information about AF	1 (3.4)	0
Wanted to improve condition	1 (3.4)	0
Dissatisfied with NHS diagnosis	1 (3.4)	0
To help NHS by seeking alternative treatment	1 (3.4)	0
Wanted to find out more about comp. therapies that might help	1 (3.4)	0
To find a way to give myself control	1 (3.4)	0

6.1.1.ii Qualitative analysis of reasons for participating

Reflexive thematic analysis of the 16 baseline interviews, and answers to the baseline questionnaire's free-text question (n=29), yielded four themes: **Benefit to self**; **Curiosity**; **Benefit to others**; and **Belief in complementary medicine**.

Benefit to self was the most dominant theme. Twelve participants expressed a wish for therapy, which they perceived as potentially helpful. Five participants expressed a desire to find out more about their condition, and saw this as a reason for participating in the study:

> I thought my palpitations were a symptom of menopause rather than an actual condition. Didn't know much about it (1/856/A)

> When I got the initial letter I… thought… it would be nice to know more about atrial fibrillation (4/142/NT)

Eight participants were dissatisfied with their current treatment, particularly wishing to reduce or stop taking medication:

> If I can find an alternative to taking medication… I'd work on it… So I could get rid of all that lot… and do something else, I would do that, because I don't like taking medication (2/163/A)

> I would just like to not be on the pills (2/515/UC)

Under the theme of **Curiosity**, participants talked about curiosity or interest focused on acupuncture in particular, the placebo effect, and complementary medicine in general:

> I was intrigued about the acupuncture side of things, so that was my… goal… to try the acupuncture (3/641/A)

> I thought that's interesting to do, to be able to compare whether the complementary techniques can add to what is out there – that can only be positive (4/142/NT)

Under **Benefit to others**, participants discussed their belief that it was good to get involved in research, and that if alternative treatments could be found for AF it would help the NHS: "The NHS is stretched and a successful additional treatment that aleviates [sic] my symptoms is a benefit" (3/641/A). Participants most often wanted to help others with AF (10 participants):

> If your study, it helps people like me in the future, have symptoms relieved a bit quicker, then fantastic (2/639/UC)

> It's not just for me … cos there's lots of people have this thing (2/163/A)

> Mainly to develop better cures for the problem (3/978/A)

Belief in complementary medicine showed participants to be either open-minded or positive about complementary medicine:

> It's worth really believing, it sounds really… gullible in a way but it… doesn't matter (2/761/A)

> They've done it for thousands of years, so there's gonna be something to it. You don't go sticking pins in people for thousands of years without any effects (2/163/A)

This disposition arose from a variety of reasons including the use of complementary therapies in interviewees' work environments, own previous experience of therapies, and the endorsement of family members:

> [My wife]'s done a lot of acupuncture… and swears by it, and says you really should do it, and I keep thinking yes I should (4/385/NT)

6.1.2 Objective 1b: Participants' reasons for declining to participate

This domain was answered using only qualitative data from participants who declined to take part (as distinct from those excluded by the eligibility criteria). Data was mainly collected from notes taken by the researcher during the queries phone call, and also from permission-to-approach (PtA) forms, the consent form and the screening call. Two participants declined by text following unsuccessful attempts to place a queries phone call.

A very small amount of data was collected to answer this domain, meaning that reflexive thematic analysis was not advisable (Byrne, 2022). Data was collated in **Table 23**. Reasons are paraphrased.

Table 23: Patients' reasons for declining to participate

	Patients declining for this reason (total n=16)
No computer, internet or skills	3
Not willing to have acupuncture	2
Contracted COVID-19	2
Not willing to have NT	1
Pacemaker fitted recently	1
Could not attend in person (has no car)	1
Could not attend in person (has family member who cannot be left alone)	1
Busy life / could not give time needed	1
Unavailable for treatment (spends much time abroad)	1
Not wishing to wear the CardioSTAT® monitor	1
AF symptoms recently resolved following procedure	1
Recently-diagnosed illness	1

6.1.2.i Effect of the pandemic on willingness to participate

Data was drawn from the permission-to-approach (PtA) form and the queries phone call to understand attitudes to COVID-19 in relation to the study.

No PtA form named COVID-19 as a reason for declining. It is possible that some declining patients who returned a PtA form may have felt COVID-19 risk to be a factor but did not name it; it is also possible that some patients who did not return a PtA form may have felt COVID-19 risk to be a factor.

During the queries phone call, one patient disclosed that they had contracted COVID-19 and declined to take part. The queries phone call also revealed anxiety on the part of another patient regarding possible transmission during face-to-face appointments if randomised to the Acupuncture group, but this patient did not decline to take part.

Qualitative data was collected regarding participants' attitudes to possibly contracting COVID-19 as a result of being in the study, from the baseline assessments (carried out between 22nd November 2021 and 8th February 2022). This exercise was somewhat redundant with regard to the effect of the pandemic on willingness to participate, since participants had already agreed to take part and therefore a degree of risk acceptance could be assumed. Nonetheless, this allowed analysis of participants' (as opposed to non-participant patients') feelings and attitudes towards COVID-19 risk from the study.

Reflexive thematic analysis of all data revealed largely homogeneous results, with just two themes. The first of these was **Concern about Risk from Participation**. One participant mentioned the anxieties of "mixing with others not in my bubble who may not be vaccinated or taking precautions" (1/464/NT). The remaining participants expressed reasons for having little or no concern, including their own vaccination status (11 participants): "I'm vaccinated up to the eyeballs at the moment" (4/272/NT); "I am fully vaccinated" (4/227/UC); "I've been vaccinated and boosted" (2/136/A). Participants were also confident due to taking their own precautions (11 participants); and the perception that COVID-19 risk had been considered or designed out of the study (10 participants). Eight participants compared the study risk to risks in other areas of their lives:

> [I expect] the therapists… [will be] very clued-up on what needs to happen basically. I'd feel a lot safer there… than [laughs] going to Waitrose (4/385/NT)

The second theme was **Living with COVID**. Participants expressed their attitudes towards the pandemic as the backdrop to the trial, including the need to "keep things in perspective" (2/515), feeling that "we're all going to catch it at some stage" (1/884/UC), and their acceptance that there was "a degree of risk in everything you do" (2/639/UC). One participant felt "a little bit blasé about it now" (1/557/UC) and three others expressed the opinion that it was time to return to life as normal:

> I feel we need to get on with life and not worry too much about illness (4/113/A).

From the data available, it would appear that COVID-19 was not a significant factor negatively affecting willingness to participate.

6.1.3 Exploratory analysis: Patient preference at pre-consent stage

Patient preference was not a subject of active investigation at pre-consent stage. However, notes taken by the researcher during the pre-consent queries phone call (n=56), together with returned permission-to-approach forms and consent forms, revealed patients' voluntary expressions of preference. Preferences included: for acupuncture (n=16); for NT (n=2); aversion to acupuncture (n=4); aversion to NT (n=9). Thirteen patients voluntarily expressed both preference and aversion; 30 expressed neither; no patient expressed a preference for usual care over either intervention. The

most frequent voluntary expression was a preference for acupuncture with a corresponding aversion to NT; this was usually linked to a belief that the patient's existing diet was of a good standard and a consequent feeling that NT was not of interest. Of the total number of patients expressing either or both preference or aversion (n=26), eight went on to give consent and were randomised.

6.1.4 Objective 1c: Number of participants randomised from the total eligible

Table 24 shows the numbers of eligible participants through the various stages of recruitment, with percentages relative to the total identified by the PICs. PIC screening identified an initial 220 potential participants, which resulted in 30 randomisations (13.6%, or a ratio of ≈1:7). This represented an average of 0.028% ± 0.009 of GP list size.

Table 24: Eligible participants at each stage of recruitment

	Identified total carried forward	% of total identified	% of eligible total randomised
PIC screening	220	–	–
Completed permission-to-approach forms	74	33.6%	–
Completed consent forms	37	16.8%	–
Eligible after consent forms received	33	15.0%	–
Eligible after screening call	31	14.1%	–
Randomised	30	13.6%	96.8%

6.1.5 Objective 1d: Effect of the COVID-19 pandemic on participants' willingness

COVID-19-related feasibility was not treated as a separate objective. Results for this domain are incorporated within domains 1a, 1b and 1c above.

6.1.6 Objective 1e: Practitioners' willingness to participate

This domain considers practitioners' willingness to participate. Santé-AF's interventions were delivered by private practitioners; the availability and willingness of eligible practitioners was therefore considered an important element of feasibility. Data was gathered from exit interviews held after the intervention period (May/June 2022).

The six recruited practitioners discussed a variety of reasons for participating. Reflexive thematic analysis yielded five themes: **The value of research**; **Community**; **Self-development**; **Working with the researcher**; and **Fees**.

Under **The value of research**, practitioners discussed their perceptions of research, seeing it as "beneficial" for the profession and for people with AF (P2/A), "fascinating" (P4/NT), and "a thrill" (P5/NT); "I felt like I was doing something really worthwhile" (P5/NT); "I will contribute to something that [people with AF] value" (P6/NT). Two NTs observed that there were "very few studies done with nutritional therapy" (P5/NT, P6/NT), and felt a responsibility to participate for that reason.

There was also anticipation of being part of a **Community**. Practitioners cited the nature of their work as a series of one-to-one appointments that could leave them feeling isolated, and looked forward to having a connection with professional colleagues as a counterbalance:

> [The] working with colleagues thing… it's nice to have that working together aspect. We kind of miss that in our profession" (P1/A)

> [It's] something bigger than me… it wasn't just about what I was doing in my little cubby-hole. [I thought it would be] nice because it feels as if you were part… of a community" (P5/NT)

Four practitioners saw their participation as **Self-development**: an opportunity to extend their professional and personal skills or attributes. One had been considering involvement in research and wanted to observe the process of a trial run with NIHR and NHS involvement (P3/A). Another felt that, after a long career, she wanted to be "challenged, but in a really kind of supportive way… doing it alongside [other] practitioners" (P1/A). For another, self-development was less professional than personal:

> [I'd been invited before] to do trials and I never had the confidence… I feel really confident in my treatments now… so I just thought… if I do this, I'll feel so good, you know… I felt like [it could be] a golden achievement personally (P2/A)

Under **Work with the researcher**, practitioners across both therapies were explicit that existing relationships with the researcher were an inducement to participate:

> I felt drawn to it… I thought "this isn't a scary research lady at a scary university, doing a scary thing, this is a lovely lady that I can work with, and learn stuff", so that drew me (P2/A)

> I think it helped, knowing who you are and that we could come to you if there was anything… you definitely need to have that face you trust (P4/NT)

> I respect you to know, and as a researcher… You asked for honest! (P6/NT)

Acupuncturists in particular were attracted to the study by the researcher's professional qualification:

> It kind of felt like a proper acupuncture trial because you are a real acupuncturist doing it… It kind of adds that sense of there's somebody with a passion for this, who knows about this medicine (P1/A)

> I understand that you've got to sit on the fence but you know, it still mattered to me that you're an acupuncturist. You just… get it. We talk the same language (P2/A)

> I think… you sympathise with [the Chinese medicine] approach… your professional understanding as well as your skill as a researcher… I dive in without hesitancy (P3/A)

Fees were, in general, not a significant inducement to participate; reasons for this differed according to the therapy. Acupuncturists found other aspects of participation to be equally or more valuable than the fees:

> It's important to be recognised and valued, so the money is a part of that… but there were so many better reasons why I wanted to do it… the connections… working with you… the condition itself… to be challenged (P1/A)

> I didn't care about the money at all… for the altruistic sense of "this is research" I probably would have done it for free (P2/A)

> It's a really valuable experience… What? I get paid? Thank you so much! (P3/A)

The NTs also regarded other aspects of the study as valuable, but not necessarily more valuable than the fees. This was partly because fees were comparable with, but not significantly in excess of, usual rates:

> £114 per consultation isn't so [different]… there are NTs that charge an awful lot more, but presumably they wouldn't agree to do it at these sort of prices. But for me, it was worthwhile money-wise (P4/NT)

> It didn't feel like it was too far under the market rate… and because it was also a trial, there's a bit of give and take (P5/NT)

> I would charge less than £114… I'm going to raise it a bit… I probably charge too little (P6/NT)

Other reasons for being willing to participate included the absence of marketing and promotional work required to secure clients (P4/NT); and the perceived endorsement from being a practitioner in a study, especially one run by a university trials unit (P2/A, P3/A, P4/NT):

> The fact that it is the University of York, which has a really good name, and it's a piece of research that is attached to the university, that just gives it extra weight. So there is almost a vanity element to that (P4/NT)

Practitioners were asked about the effect of the pandemic on their willingness to participate, but had very little to report: "I don't think the pandemic had the slightest effect… I would have wanted to

do it, COVID or no COVID" (P4/NT); "If you'd asked me back in 2020 I'd have probably said no because after [the first] lockdown it was like the whole world wanted acupuncture… but it quietened down" (P2/A).

6.1.7 Objective 1f: Effect of the pandemic on practitioners' willingness

COVID-19-related feasibility was not treated as a separate objective. Results for this domain are incorporated within domain 1e above.

6.1.8 Objective 1g: PICs' willingness to participate

Participant Identification Centres (PICs) were considered to be a type of participant in the study, as their involvement was crucial in being able to recruit sufficient participants. For this reason, PICs' willingness to take part was considered part of recruitment-related feasibility objectives.

All primary care practices in the Vale of York (n=23) were invited to become Participant Identification Centres (PICs) between 25th August and 21st October 2021. Five Expressions of Interest (EOIs) (21.7%) were received, and four (17.4%) were recruited. The fifth did not respond to follow-up emails, so it is not possible to understand the reasons for non-recruitment.

Exit interviews were conducted with the staff who had carried out the screening at each practice. The small amount of data made thematic analysis inadvisable (Byrne, 2022); instead, data is narratively described below.

The four PICs expressed a range of reasons for responding to the initial invitation. These included "supporting local research" (PIC3); "[the study] was easy to understand and navigate" (PIC4); and the fact that the practice's list included "quite a large AF burden and it's nice to offer those patients something" (PIC3). Two PICs felt their patients would like to access the therapies in the study:

> I can think of half a dozen right away who would really like to have either of these therapies, the acupuncture in particular (PIC1)
>
> It seems to me they'd jump at the chance to look at things like nutritional adjustment… [and] especially acupuncture (PIC3)

Two PICs appreciated the responsiveness of the researcher during preliminary contact, which supported the decision to participate:

> When you're trying to do something… if you've got a question, and the answer might come a few days down the line when you might not have any more time to complete that task… the fact that you answered so promptly, that was very helpful. It was all very straightforward (PIC1)

> I think you'd made it as easy as it could have been… you've been very contactable so I didn't think there'd be any issue in asking you if there were any problems (PIC4)

All four PICs acknowledged that pressures on primary care (including but not limited to the COVID-19 pandemic and the vaccination delivery programme) had delayed their response to the CRN's initial invitation, and their start on the participant identification process. Short exit interviews carried out post-recruitment with each PIC yielded the following comments:

> It is quite bad right now… lots of competing pressures and the summer break, and something like this can easily slip (PIC1)

> At the present time we just have no time whatsoever for anything like this at the moment. I'm very fortunate that we have protected research hours (PIC2)

> Huge pressures… we're trying to deliver good chronic disease care alongside urgent care, as well as trying to roll out both COVID and influenza vaccines (PIC3)

> There's a lot going on, of course, and we're always up against that but it is quite strenuous at the moment what with vaccination in particular (PIC4)

One GP had recommended the study to another York primary care practice, but disclosed to the researcher their knowledge that "[pressures including COVID] mean they don't have the capacity" (PIC1).

The CRN Study Support Service offered to email all non-responding primary care practices requesting their reasons for non-participation, but the researcher was not notified of any responses.

6.1.9 Objective 1h: Effect of the pandemic on PICs' willingness

COVID-19-related feasibility was not treated as a separate objective. Results for this domain are incorporated within domain 1g above.

6.1.10 Synthesis of objective 1: Participants' willingness to take part

The joint display table (**Figure 8**, overleaf) synthesises the qualitative and quantitative data regarding participants' willingness to take part (i.e., not including practitioners or PICs). Quantitative data is represented as participants' most important reasons for taking part; this is shown alongside consonant or dissonant themes from the qualitative data.

Objective 1: Participants' willingness to take part – Joint display table

QUANTITATIVE RESULTS		QUALITATIVE RESULTS: Reasons for taking part	
Dissatisfaction with NHS treatment	0* ↓	↑ 8†	It seemed like a good opportunity to see if something could help with the AF other than constantly having drugs or… going to the tough level of having a pacemaker at sometime or other (3/641/A)
Curious about medical research	4 ↑	↓ 0	
Curious about acupuncture / Wanted acupuncture, hoping it would cure AF	7 ↓	↑ 9	I'm interested in whether acupuncture could be helpful (2/515/UC) I feel I would not like having acupuncture… so I think it's best you invite someone else to take part in your study (4/418)
Curious about nutritional therapy	1 ↓	↑ 4	[the other therapy] was to do with diet and weight… and I just thought it sounded a very interesting other therapy. (1/661/A)
Curious about complementary therapies in general	4 ↑	↓ 1	I'm curious, because I've never been… one to explore or be particularly interested in [complementary therapies] (4/142/NT)
Wanted to have some free treatment that might help	2 ↓	↑ 5	Hopefully maybe acupuncture might help as well, and it might get rid of it, or you know, the dietary one, it might help me control my diet a little bit better (1/884/UC)
Wanted to help other people with AF by contributing to the knowledge base	6 ↓	↑ 10	I think there's an interest that I'd be doing something good to help other people that have got this. (1/557/UC)
Wanted chance to have AF monitored by a CardioSTAT® ECG device	3 ↑	↓ 1	I would just like to say at this point, I do not want to wear the CardioSTAT monitor (3/651)
Other: Wanted more information about AF	0 ↓	↑ 5	I hadn't had any information about AF from any medical professional for months, and months and months, it was as if… I hadn't existed, to some extent (4/385/NT)
Other: Wanted an alternative to medication	1 ↓	↑ 7	Would love to come off some of my medication if at all possible (3/684/A)
Other: To help NHS by seeking alternative treatment	0 ↓	↑ 1	[I hope it can] help the NHS become more efficient at dealing with it in some way… often these things end up in actually cost less if you know how to deal with something efficiently (4/142/NT)

** n of 29 participants noting this as the most important reason for participating*
† n of 29 participants who commented on this in interview, or in free-text questions in baseline questionnaire or other documents
= consonant feeling, belief or opinion; = dissonant feeling, belief or opinion

Figure 8: Objective 1 synthesis – participants' willingness to take part

6.1.11 Assessment of feasibility for objective 1

The feasibility threshold was set at ≥90% of eligible participants randomised. 96.8% of those identified as eligible at the end of the full screening process were randomised. By this threshold, objective 1 can be judged feasible.

6.2 Objective 2: Appropriateness of eligibility criteria

This objective focused on the study's eligibility criteria. It was divided into four domains, one of which focuses on practitioners' eligibility. In this objective, the word "appropriateness" was defined as the ability of the criteria to produce a sufficient cohort of patients (or practitioners) to meet the sample size.

6.2.1 Objective 2a: Number of participants excluded by each eligibility criterion

Four PICs carried out a database search on their lists, with subsequent screening, to identify patients conforming to those eligibility criteria that were noted on the medical record. Later stages of the recruitment process, particularly the screening call, identified further ineligible patients. Exclusions from all stages have been collated and are shown in **Table 25** which sets out the total number of exclusions as a result of each eligibility criterion, alongside the percentage of the identified population that they represent. The final total of eligible participants was 220.

Three extra eligibility criteria were added to the study to minimise COVID-19 infection risk (INC6 and INC7, EXC11). These appear to have had minimal effect on the study, excluding just 40 participants in total (although it is not known how many participants self-excluded on the basis of these criteria without notifying the study).

Table 25: Numbers of participants excluded by each eligibility criterion

Total number of patients with diagnosis of AF included by PICS		2,744	100.0%
Criterion #	Description	Number excluded	% of AF population excluded
INC1	Aged ≥45 ≤70	2,031	74.0%
INC2	Diagnosis of AF ≥6 months ≤60 months previously	409	14.9%
INC3	Stroke prevention measures offered/applied where indicated	4	0.2%
INC4	Self-detectable paroxysmal AF of at least weekly frequency	13	0.5%
INC5	Owner of, and able to use, a mobile phone	0	–
INC6	Home broadband of sufficient capacity	1	0.0%
INC7	Owner & able to use monitor for video conferencing OR study iPad	2	0.1%
INC8	Willing to have acupuncture/NT alongside UC or UC alone	3	0.1%
INC9	Willing to travel for acupuncture appointments (subsidised travel)	1	0.0%
INC10	Willing to wear & return CardioSTAT ambulatory ECG for 2 x 7 days	1	0.0%
INC11	Speak English sufficiently to engage with interventions/assessments	0	–
INC12	Able to give informed consent	4	0.2%

Table continued overleaf

Criterion #	Description	Number excluded	% of AF population excluded
EXC1	Valvular AF	6	0.2%
EXC2	Pacemaker or other active implanted monitor	19	0.7%
EXC3	Kidney disease Levels 4 or 5	4	0.2%
EXC4	Diagnosis of severe or terminal illness	4	0.2%
EXC5	Diagnosis of blood clotting disorder	1	0.0%
EXC6	Contraindicated to exercise	1	0.0%
EXC7	Diagnosed with eating disorder past or present	1	0.0%
EXC8	Pregnant or trying to conceive	0	–
EXC9	Taking part in other research likely to affect outcomes/unsafe	0	–
EXC10	Current or recent acupuncture/nutritional therapy	0	–
EXC11	Shielding, vulnerable or extremely vulnerable to COVID-19*	37	1.4%
EXC12	Using TENS machine or other energy delivery monitor	1	0.0%
EXC13	Patients excluded by GP for other clinical reasons	18	0.7%

* these categories were no longer in use by the time study recruitment began in September 2021 (NHS Digital, 2022). They were retained as they had been approved by the HRA London Surrey REC in Amendment 1.

Four of the 30 participants (13.3%) were randomised in violation of the eligibility criteria. In the first case, the participant challenged the exclusion criterion (EXC4: Diagnosis with terminal or severe illness). This participant had a diagnosis of prostate cancer on active surveillance but was keen to join the study. The advice of academic supervisors was sought; this suggested that the participant should be randomised and the criterion reconsidered for a future trial. The researcher queried the participant's eligibility with the PIC, which replied: "[it's] a bit of a grey area as to whether it's terminal, and it's definitely not going to stop him doing anything on the trial" (Charlesworth, 2021); their clinical judgement had therefore overridden this exclusion criterion.

The remaining three participants who violated eligibility criteria were effectively randomised in error as they disclosed information during the study that would have rendered them ineligible had it been disclosed before randomisation. One participant disclosed a diagnosis of permanent AF, where the study's INC4 stipulated paroxysmal AF only; two participants disclosed an AF onset date longer ago than the 60 months stipulated by INC2. The data of all three participants was retained in analyses on the grounds that there were no clinical concerns regarding participation, and the characteristics were unlikely to render the participants systematically different from others in feasibility terms; the randomisations were accepted and correct baseline data was recorded according to good practice (Yelland et al., 2015).

6.2.2 Objective 2b: Similarity of participant characteristics to other AF cohorts

This feasibility domain was originally intended to detect whether the eligibility criteria had recruited a cohort demographically and clinically similar to those of comparable AF studies, and a progression threshold was set of ≤20% difference between Santé-AF and the comparators. However, the analysis was judged to be of little use to a future trial in the context of other changes recommended to eligibility criteria, and is therefore not reported here. Results are reported in **Appendix D** for completeness.

6.2.3 Objective 2c: Effect of extra eligibility criteria added due to the pandemic

COVID-19-related feasibility was not treated as a separate objective. Results for this domain are incorporated in objective 2a above.

6.2.4 Objective 2d: Number of practitioners eligible and reasons for non-eligibility

An internet survey was conducted in March 2021 to identify practitioners who were members of either the British Acupuncture Council (BAcC) or the British Association for Nutrition and Lifestyle Medicine (BANT) based locally to the study centre. Twenty-three practitioners were identified (14 acupuncturists and 10 nutritional therapists (NTs)) and emailed with a short information sheet and an invitation to submit expressions of interest (EOIs). Nineteen responses were received (11 acupuncturists, eight NTs). Following receipt of EOIs, all responders completed an online eligibility questionnaire. 27.3% of the total responding acupuncturists and 37.5% of the total responding NTs were eligible to participate. Eligibility status and reasons for non-eligibility are given in **Table 26**. All documents can be found in **Appendix A**, Practitioner documents section.

Table 26: Practitioners' eligibility and reasons for non-eligibility

#	Therapy*	Eligibility status	Reasons for non-eligibility
1	A	Eligible	n/a
2	A	Eligible	n/a
3	A	Eligible	n/a
4	NT	Eligible	n/a
5	NT	Eligible	n/a
6	NT	Eligible	n/a
7	A	Non-eligible	Moving practice to a non-local area
8	A	Non-eligible	Moved practice to a non-local area during lockdown
9	A	Non-eligible	Practice too busy to participate
10	A	Non-eligible	Non-TCM acupuncture style; left BAcC during pandemic

Table continued overleaf

#	Therapy*	Eligibility status	Reasons for non-eligibility
11	A	Non-eligible	Left BAcC during pandemic
12	A	Non-eligible	Needs four-six weeks off at Christmas & summer
13	A	Non-eligible	Not able to commit to maintaining BAcC registration for 2 years after study
14	A	Non-eligible	Stopped practising during pandemic
15	NT	Non-eligible	Professional qualification not at appropriate level
16	NT	Non-eligible	Professional qualification not at appropriate level
17	NT	Non-eligible	Not in practice long enough to meet eligibility criterion
18	NT	Non-eligible	Initially eligible but clinic became too busy; practitioner withdrew
19	NT	Non-eligible	Not able to work online

* **A** acupuncture; **BAcC** British Acupuncture Council; **NT** nutritional therapy; **TCM** Traditional Chinese Medicine

6.2.4.i Exploratory analysis: Practitioner characteristics

All practitioners conformed to the practitioner eligibility criteria. A check was carried out with each professional body to confirm each practitioner's good standing and the absence or satisfactory conclusion of any investigations into professional conduct or practice.

Practitioners were all female, and had been in practice for an average length of 22.3 years (acupuncturists) or 4.3 years (nutritional therapists (NTs)). Two acupuncturists had previously taken part in trials as practitioners; one NT had trials experience through part-time employment as a research nurse but had not previously taken part in a study as a practitioner of NT.

Acupuncturists were, by chance, all based at a single clinic, situated on the A1036 approximately 1.5 miles south-west of York city centre, with private car parking; acupuncturists worked at different times from each other with some overlap. NTs worked online using a variety of videoconferencing software, email, and tools for appointment booking and online form completion.

One acupuncturist and one NT held academic posts at the study centre (the Northern College of Acupuncture (NCA)), while a further NT had previously been taught by the researcher at NCA. Additionally, all acupuncturists had a pre-existing connection with the researcher via a global acupuncture community event in mid-2020. Despite pre-existing relationships, all practitioners were recruited via the survey and invitation process.

6.2.5 Assessment of feasibility for objective 2

This criterion expressed the number of eligible participants as a percentage of those identified by the PICs, with a feasibility threshold of ≥60%. **Table 24** shows that just 31 (14.1%) of the total identified by the PICs were confirmed as eligible. By this threshold, this objective of Santé-AF was not judged feasible.

6.3 Objective 3: Participant retention

Santé-AF recruited 30 participants (the planned sample size), which included a margin for ≤20% attrition. Participants were defined as "retained" if they completed the follow-up assessment. This objective focused on the number of participants retained at various stages of the trial, and their reasons for remaining or withdrawing.

6.3.1 Objective 3a: Percentage of consented participants retained at baseline

Twenty-nine of 37 (78.4%) consented participants were retained at baseline, following four exclusions and three declines (all pre-randomisation) and one post-randomisation withdrawal due to illness (**Figure 7**).

6.3.2 Objective 3b: Percentage of randomised participants retained at follow-up

Figure 7 shows that 25 of 30 (83.3%) randomised participants were retained at follow-up after two withdrawals (one NT, one Usual Care), one discontinuation of intervention (NT), and two losses to follow-up (one NT, one Usual Care). All 12 participants in the Acupuncture group were successfully followed up, although one was unable to undertake the intervention.

6.3.3 Objective 3c: Number of compliance prompts needed

Compliance prompts were used for participants who had not returned symptom diaries and/or CardioSTAT® ECG monitors after the seven days following assessments. Analysis of this domain was carried out, but was not judged to be useful for a future trial on the basis that a future trial will use its own methods of compliance prompting. Analysis is reported in **Appendix D** for completeness.

6.3.4 Objective 3d: Participants' reasons for withdrawal

Participants' reasons for withdrawal were taken from qualitative data collected during study communications.

The first of the withdrawing participants (1/485/NT) was randomised to the NT group, but telephoned to withdraw before the baseline assessment due to a terminal diagnosis.

A second participant (2/174/NT), randomised to the NT group, became uncontactable before the intervention started and did not give a reason for withdrawing. This may have been linked to an incident during the baseline assessment, in which the participant declared that they were not taking any medications, but the assessment revealed an extremely high blood pressure reading that (with the participant's consent) was reported back to the participant's primary care practice as a red flag

and incidental medical finding. The practice contacted the participant for reassessment. It is possible that the reassessment discovered further symptoms, leading to the participant discontinuing the study without notification.

The third participant (2/122/NT), randomised to the NT group, discontinued the intervention after the first appointment and ultimately became uncontactable. In an email to the researcher, the practitioner expressed her belief that this was due to technology issues (an indirect effect of the COVID-19 pandemic):

> [2/122/NT] has had many problems with technology, including broadband and lack of experience with using the internet… Their first appointment appeared to go well, once they were able to book it with the help of their partner. We conducted the consultation on the telephone as they were not able to get Zoom working. I completed the nutritional health questionnaire for them during the appointment… as they weren't able to complete it themselves [online]… When they missed their second consultation, I had half-expected them… to have broadband or other technology issues. (P3/NT, 2022) (pronouns replaced)

Repeated attempts by the researcher to contact 2/122/NT, including phone calls, emails and a letter hand-delivered to the participant's address, were partially successful in making contact, but unsuccessful in re-establishing therapy. The participant offered no reason for discontinuing the intervention and was lost to follow-up.

The fourth participant (2/294/UC), randomised to the Usual Care group, became uncontactable after three attempts at follow-up that were each cancelled due to unpredictable demands on the participant's time. The participant was keen to complete the study:

> I'm sorry I couldn't do [the previous appointment]… I said I'd do it, so I will, of course… I wouldn't let you down. I know I haven't had anything from the study but I know… the people who don't get anything are your benchmark (2/294/UC)

After the third unsuccessful follow-up, the researcher telephoned the participant several times, but this elicited no response and the participant was eventually regarded as lost to follow-up.

The fifth participant (2/136/UC), randomised to the Usual Care group, emailed to withdraw before the intervention period began due to resentful demoralisation (Onghena, 2005; Torgerson and Sibbald, 1998). During the screening call, 2/136/UC had expressed a preference to be in the Acupuncture group and did not grasp that allocation was random despite repeated explanations:

> I would like to withdraw and I know it seems like I'm being reactive to not being picked for a treatment. In some respects yes having a random allocation is fair but when there's an assessment it would seem fairer to allocate from that (2/136/UC)

One participant (3/684/A), randomised to the Acupuncture group, was contacted by telephone when they had not booked a first appointment three weeks after receiving a randomisation notification. The participant, who lived 20 miles from the acupuncturists' premises, had experienced a change in circumstances after the baseline assessment, and was not able to leave the house for the regular extended periods required to attend appointments in person. The participant did agree to complete the follow-up assessment and was therefore treated as an active member of the Acupuncture group (i.e., not withdrawn or lost to follow-up).

No randomised participants withdrew due to contracting COVID-19 (although it may have been a factor in the unattributed withdrawals described above). Two randomised participants contracted COVID-19 during the trial (both Acupuncture group participants), but did not withdraw.

6.3.5 Objective 3e: Participants' reasons for remaining in the study

This domain was answered using qualitative and quantitative data gathered from the follow-up questionnaire and interviews.

6.3.5.i Quantitative analysis of reasons for remaining in the study

The follow-up questionnaire asked participants to nominate all that applied from a pre-defined list of reasons for remaining in the study, together with a free-text "other reasons" box. Of these, they were then asked to nominate the most important reason. Results are shown in **Table 27** (overleaf).

Table 27: Participants' reasons for remaining in the study

	n (%) participants citing this reason	n (%) participants citing this as most important reason
Dissatisfaction with NHS treatment (n=25)	7 (28.0)	0 (0.0)
Wanted to have some free treatment that might help (n=20)	11 (55.0)	3 (15.0)
Wanted to continue having AF monitored by CardioSTAT® (n=9)	4 (44.4)	1 (11.1)
Enjoying appointments (n=20)	17 (85.0)	1 (5.0)
Appointments have helped me feel better (n=20)	14 (70.0)	6 (30.0)
Wanted to help others with AF by contributing to knowledge base (n=25)	24 (96.0)	12 (48.0)
Couldn't afford treatment if not in the study (n=20)	1 (5.0)	0 (0.0)
Enjoyed working relationship with practitioner (n=20)	13 (65.0)	1 (5.0)
Didn't want to upset practitioner by leaving (n=20)	1 (5.0)	0 (0.0)
Didn't want to upset researcher by leaving (n=25)	2 (8.0)	0 (0.0)
Other:		
Curiosity about acupuncture, good opportunity to try it (n=11)	1 (9.1)	0 (0.0)
Interested to "open new doors" for self, others and NHS (n=25)	1 (4.0)	1 (4.0)
Not a quitter (n=25)	1 (4.0)	0 (0.0)
Curiosity about research/complementary therapies (n=25)	1 (4.0)	0 (0.0)

% calculated using applicable n noted in row. Applicable numbers vary according to participant sub-group allocations.

6.3.5.ii Qualitative analysis of reasons for remaining in the study

Reflexive thematic analysis of the 14 follow-up interviews, and answers to the follow-up questionnaire's free-text question (n=25), yielded four themes: **Benefit to self**, **The greater good**, **Not a quitter**, and **Negative aspects of leaving**.

The dominant theme was **Benefit to self**, in which 17 of 25 participants discussed the importance of the study benefiting them. Perceived benefits included general interest (four participants): "I found the whole thing… interesting" (2/163/A) and general benefits to themselves (three participants): "I'm there to… see what I can get out of it for myself" (3/156/A). One dissonant perspective within this theme came from a participant who felt that benefit to them was not a motivating factor:

> Whether it makes any difference to me… is not important. It will add to the knowledge for the future. I think that is key (4/142/NT)

Eight participants mentioned treatment-related reasons for remaining in the study; these are explored further under **6.4.2.iii**, below.

Under the theme **The greater good**, 14 participants from all groups voiced their perception of the study being of benefit to a wider AF community and/or a generally worthwhile endeavour:

> I think it's just good to get involved with stuff like this… because this is what changes things, isn't it? (2/163/A)

> You just do it for the greater good (4/910/A)
>
> It did create that feeling of, this is worthwhile (4/142/NT)

Nine participants had stayed in the study to help find solutions for the wider AF community:

> My findings… are obviously not unique, so I'm all for it, could help others (4/272/NT)
>
> The thought of finding something that helps is really compelling for me and others. (2/761/A)

Three of the four Usual Care group participants contributed strongly under **The greater good**, feeling they had stayed in the study to help it achieve its goals and help others with AF: "[now I've gone back into AF], hopefully the results that you get from my diary… may help you a little bit" (1/884/UC); "the only possible effect it can have is if the information I provide is of any use to anybody else in the future of the study" (2/639/UC). Participants in all groups felt they could "do some good" by contributing:

> if I would be a kind of a guinea pig and somebody benefits, then for me, that actually is a good outcome… it's a positive kind of "ooh well I've done some good" – I do so little good [laughs] (2/761/A)

The **Not a quitter** theme saw homogenous contributions from 13 participants (all from the active intervention groups) regarding their view of themselves as, on principle, "seeing [things] out" (1/557/A), "committing [myself] to it" (3/641/A), "carrying [things] through" (3/156/A) and "not a quitter… if you stand up to do something, you do it" (1/661/A):

> I used to [laughs] as a teacher go on and on about sticking at things… don't just dabble at things, get on and have a real go at it… So I could have hardly spent years teaching that and then flop at the first hurdle [laughs] in the trial. (4/142/NT)

Free-text questions and interviews gave participants the opportunity to explore **Negative aspects of leaving**. Under this theme, five participants said they would feel "disappointed" in themselves if they left, that leaving would waste their own and others' time, or stated an aversion to what they perceived as letting down either their practitioner, or the researcher, or both:

> I don't want to let [acupuncturist] down, I don't want to let [researcher] down (3/156/A)
>
> I don't want to let [NT] down… I definitely wanted to do what she'd suggested, because she'd obviously put a lot of time and effort into it (4/385/NT)

One participant thought of leaving after experiencing painful acupuncture:

> It made me jump… and afterwards I came away thinking… I bet loads of people having had an experience like that, go, do you know what, I'm not going back… and I

> told myself… the last thing I do is, just because… a few needles hurt, that isn't enough to bottle it (2/761/A)

Dissonant views within this theme included a participant who said they would have left had they seen no benefit from the treatment (2/256/A).

Exploratory analysis: Where Usual Care participants' (n=4 at follow-up) reasons for remaining in the study were congruent with treatment group participants' reasons, they were included with those analyses (above) but a separate, self-contained analysis of *all* Usual Care group participants' reasons for remaining was of interest to a future trial. However, one Usual Care participant was not an interviewee and contributed only two qualitative comments on the follow-up questionnaire, neither of which concerned retention. The small amount of data collected from the remaining three Usual Care participants made reflexive thematic analysis inadvisable (Byrne, 2022); instead, these were tabulated (in paraphrased form) in **Table 28** (overleaf).

Table 28: Usual Care group participants' reasons for remaining in the study

	n (%) of 4 Usual Care participants remaining in the study for this reason
Helping the study, thereby helping others with AF (1/884/UC) (2/639/UC) (2/515/UC)	3 (75.0)
Convenience of not having to do anything (1/884/UC) (2/639/UC)	2 (50.0)
May be selected for a future large-scale trial (1/884/UC)	1 (25.0)
Acceptance that not being selected for a treatment group is part of being involved (2/515/UC)	1 (25.0)
Have gone back into AF so feel my symptoms are of use to the study (1/884/UC)	1 (25.0)

6.3.6 Objective 3f: Effect of the pandemic on participant retention

COVID-19-related feasibility was not treated as a separate objective. Results for this domain are incorporated within domain 3d above.

6.3.7 Synthesis of objective 3: Participant retention

The joint display table (**Figure 9**, overleaf) synthesises qualitative and quantitative data for participant retention. Quantitative data represents participants' most important reasons for remaining in the study; this is shown alongside consonant or dissonant themes from the qualitative data.

Objective 3: Participant retention – Joint display table

QUANTITATIVE RESULTS		QUALITATIVE RESULTS: Reasons for remaining	
Dissatisfaction with NHS treatment	0* ↓	↑ 1†	I believe there are better ways of dealing with AFIB apart from just taking medication (2/163/A)
Wanting to have some free treatment that might help	3 →	← 3	I did want there to be an improvement (2/761/A) Not because it was free [but] because it might help (2/256/A)
Wanting to continue having AF monitored by CardioSTAT® ECG device	1 ↑	↓ 0	
Enjoying appointments	1 ↓	↑ 4	I've enjoyed the process. And I was looking forward to my appointments every week (4/910/A)
Appointments have helped me feel better	6 ↑	↓ 5	Bottom line, I found the acupuncture beneficial. Simple as that (3/641/A) Whether it makes any difference to me... is not important (2/761/A)
Wanting to help others with AF by contributing to knowledge base	12 ↑	↓ 9	Something good might come out of it... for other people (1/661/A)
Trial is generally worthwhile for the "greater good"	0 ↓	↑ 14	This could yield something useful... This is well worth doing... This is worthwhile (4/142/NT)
Enjoy my working relationship with practitioner	1 ↓	↑ 9	Couldn't wish for a nicer person... she makes you feel very, very comfortable (3/156/A) I didn't feel very included... I just didn't really feel... I was getting an understanding of what was happening (1/557/UC)
Other: Curiosity about acupuncture, good opportunity to try it	0 ↓	↑ 2	Always been interested in acupuncture + good opportunity to try it & help others (1/856/A)
Other: Interested to "open new doors" for self, others and NHS	1 ↑	↓ 0	
Other: Not a quitter	0 ↓	↑ 13	If you embark on something, you stick it through. Otherwise it's not worth doing it in the first place (4/910/A)
Negative aspects of leaving / Not wanting to let therapist/researcher down	0 ↓	↑ 5	I don't like to let people down (2/964/NT) I'm one of these people...I've got a trait that tries to please... and erm, I do recognise it sometimes, but I was conscious of that, so... that wasn't part of it (2/761/A)

** n of 25 participants noting this as the most important reason for remaining in the study*
† n of 25 of participants who commented on this in follow-up interview, or in free-text questions in follow-up questionnaire or other documents
= consonant feeling, belief or opinion; = dissonant feeling, belief or opinion

Figure 9: Objective 3 synthesis – participants' reasons for remaining in the study

6.3.8 Assessment of feasibility for objective 3

The study's sample size calculation allowed for an attrition level of 20% (six participants of the cohort of 30). The feasibility threshold for this objective was therefore set at ≥80% of randomised participants retained. At follow-up, Santé-AF retained 25 participants from the original randomised 30 (83.3%). By this threshold, this objective of Santé-AF was judged feasible.

6.4 Objective 4: Intervention acceptability

This objective focuses on the acceptability of acupuncture and nutritional therapy (NT) to participants. It has three domains.

6.4.1 Objective 4a: Participant satisfaction with group allocation

This domain was answered with quantitative data taken from an SMS poll and qualitative data from the follow-up questionnaire and interviews.

6.4.1.i Quantitative analysis of participant satisfaction with group allocation

An SMS poll was sent to all participants after group allocation was notified (n=29), requesting their level of satisfaction with group allocation on a scale of 1-10 (1 = extremely unsatisfied). Twenty-eight participants responded.

The number of randomised participants showing a high level of satisfaction with their group allocation (defined as ≥ 7 on the 10-point scale) was 21, or 75.0% of 28 participants. The results are shown by group in **Figure 10**, overleaf.

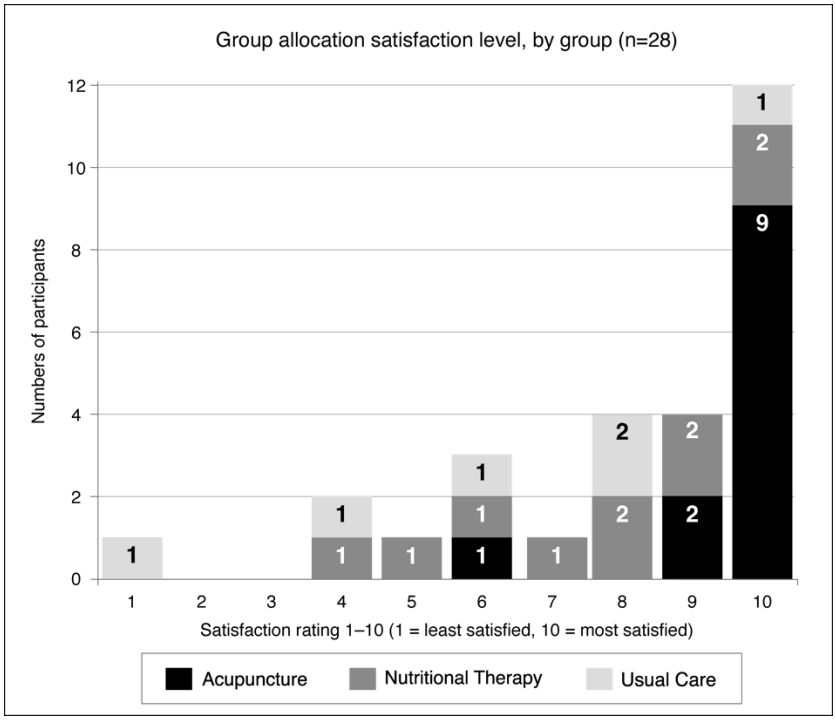

Figure 10: Allocation satisfaction level (shown by group) for n=28 participants

6.4.1.ii Qualitative analysis of participant satisfaction with group allocation

Qualitative data regarding allocation emerged from the follow-up questionnaire and interviews. Reflexive thematic analysis was not possible due to a very small amount of data (Byrne, 2022); reasons for being satisfied or otherwise with group allocation are described here.

Participants randomised to the Acupuncture group were mostly "pleased" (1/557/A); "very pleased… would have learnt a lot on the nutrition side [but] I'm more interested in the acupuncture" (2/761/A); "great… I was very open to acupuncture" (3/641/A). A dissonant view came from a participant who "had [acupuncture] on my back, and I got no benefit from it… but I was willing to give it a try" (3/156/A).

Participants randomised to NT were, in general, less satisfied with their allocation than acupuncture participants. Three expressed a preference for acupuncture: "I wanted to try the acupuncture" (4/272/NT); "I was hoping to do acupuncture that is all" (4/840/NT); the third had hoped for acupuncture, but was satisfied with allocation after reflecting that "nutritional therapy could be of a bigger benefit to me because… I was generally losing weight very slowly" (4/385/NT). The fourth "felt it unlikely that the therapy would do a lot for me" (4/142/NT).

Usual Care group participants were "disappointed" (2/639/UC); "rejected" (1/884/UC); "disappointed but philosophical… was hoping to receive a treatment that might have helped" (2/515/UC).

6.4.2 Objective 4b: Acceptability of intervention to participants

This domain was answered using quantitative and qualitative data collected from the follow-up questionnaire and interviews.

6.4.2.i Quantitative analysis of acceptability of intervention

The follow-up questionnaire asked participants in the active intervention groups (n=20) to indicate the overall acceptability of their therapy on a scale of 1–7 (where lower numbers = greater acceptability). The results are shown per group in **Figure 11**. The average acceptability per group was 1.5 (Acupuncture) compared with 2.1 (NT).

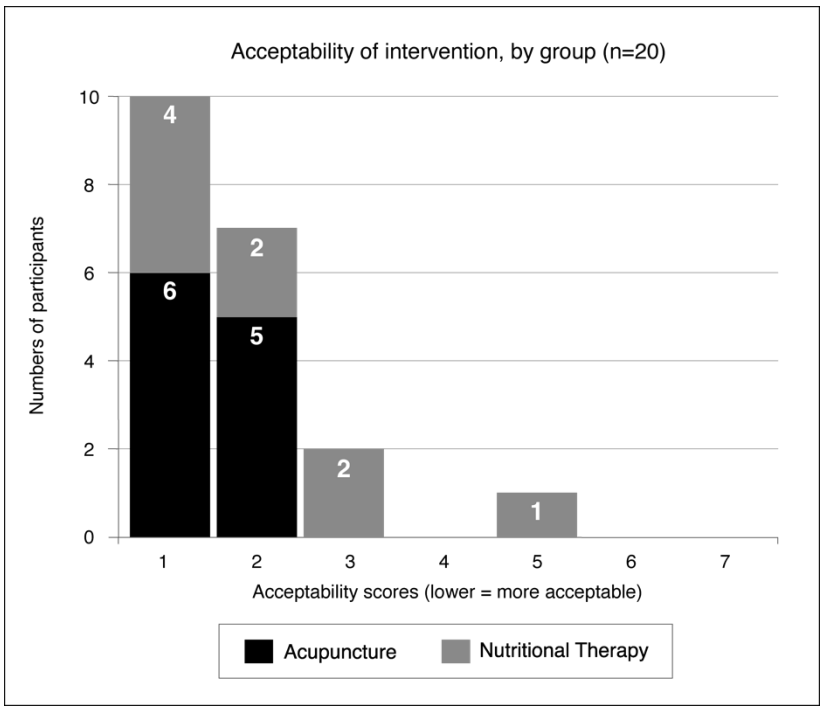

Figure 11: Acceptability of intervention (shown by group) for n=20 participants

6.4.2.ii Exploratory analysis: Appointment attendance

An exploratory analysis of data from practitioner log books was carried out to determine the level of attendance at appointments for each therapy, as a proxy for acceptability. Attendance was counted

as number of appointments attended from the total possible for each therapy (i.e., reschedules were not counted as non-attended). Data is included for participant 3/684/A who could not attend appointments due to family circumstances but agreed to complete follow-up; data is not included for participants who withdrew before the intervention began. Results are shown in **Table 29**.

Table 29: Attendance totals, and reasons for non-attendance

Practitioner, therapy, participant	Rescheduled	Cancelled and not rescheduled	% attended by this participant	Reasons for reschedule, cancellation or non-attendance	Average % attendance for this practitioner
P1/A					96.9
3/978/A	0	0	100.0%	n/a	
2/256/A	1	1	87.5%	COVID-19	
1/856/A	1	0	100.0%	Family illness	
4/113/A	0	0	100.0%	n/a	
P2/A					75.0
2/163/A	0	0	100.0%	n/a	
3/156/A	0	0	100.0%	n/a	
4/910/A	0	0	100.0%	n/a	
3/684/A	0	8	0.0%	Family circumstances	
P3/A					93.8
1/661/A	0	1	87.5%	Other illness	
1/557/A	0	1	87.5%	COVID-19	
2/761/A	0	0	100.0%	n/a	
3/641/A	0	0	100.0%	n/a	
P4/NT					83.3
2/481/NT	0	0	100.0%	n/a	
4/385/NT	0	0	100.0%	n/a	
2/122/NT	0	2	33.3%	Participant uncontactable	
4/693/NT	0	0	100.0%	n/a	
P5/NT					100.0
1/464/NT	0	0	100.0%	n/a	
4/272/NT	0	0	100.0%	n/a	
4/142/NT	0	0	100.0%	n/a	
P6/NT					100.0
2/964/NT	0	0	100.0%	n/a	
4/840/NT	0	0	100.0%	n/a	
3/806/NT	0	0	100.0%	n/a	
Total % appointments attended (Acupuncture)					88.6
Total % appointments attended (NT)					94.4
Mean % attendance, both therapies					91.5

6.4.2.iii Qualitative analysis of acceptability of intervention

Reflexive thematic analysis of the 14 follow-up interviews, and answers to the follow-up questionnaire's free-text question (n=20), found six themes: **Intervention effects**, **Therapy experience**, **Practitioner relationship**, **Logistics**, **Effect of COVID-19** and **Overall**

acceptability. Data was analysed together and per group to detect reasons for any differences in acceptability between groups.

The researcher's positionality (as an acupuncturist) was brought actively to mind during this analysis (Braun and Clarke, 2021, 2019). A reflexive journal was used to note interpretations; some interpretations were discussed with NT practitioners for triangulation.

Intervention effects: Eighteen participants commented on acceptability in terms of their perception of their intervention's effects, which were mostly felt to be positive: "I do think it's beneficial" (2/163/A); "I did begin to feel better" (4/385/NT); "Bottom line, I found the acupuncture beneficial" (3/641/A). More specific effects were judged in a variety of ways including (perceived) effect on AF symptoms, effect on other symptoms, or effect on general health and wellbeing. Participants noted improved AF symptoms including exercise tolerance (2 Acupuncture, 1 NT); dyspnoea (3 Acupuncture, 2 NT); and palpitations (4 Acupuncture, 2 NT). Three participants (1 Acupuncture, 2 NT) reported fewer AF episodes, and two further participants (both Acupuncture) were not sure whether they were experiencing fewer episodes or simply had not noticed them:

> Certainly when I first went and I was lying on the couch, I could feel the palpitations very strongly. Towards the end, couldn't feel them at all (1/661/A)

> I'm aware that my beat is always bad… it's that missing the beat, sometimes, that you do notice, and I haven't noticed it as much in the last few weeks (2/256/A)

Positive effects on other symptoms included musculoskeletal problems (3 Acupuncture, 1 NT); (positive) weight loss (3 NT); "mental attitude" (2 Acupuncture); peripheral oedema (1 Acupuncture); blood pressure (1 Acupuncture); Irritable Bowel Syndrome (1 NT); bowel irregularity (1 NT) and Parkinson's tremor (1 Acupuncture). Interventions were also noted as having positive effects on general health and wellbeing (5 Acupuncture, 2 NT), and also on sleep (4 Acupuncture, 1 NT) and energy (5 Acupuncture, 2 NT). One participant identified improvements in energy that they felt may have improved AF symptoms: "I did begin to feel better… that would have helped my AF, I feel certain." (4/385/NT).

Participants also described personal changes that they attributed to their intervention, finding the intervention more acceptable as a result:

> I feel more confident in myself now… it's nice to come back into this confident zone again… So yeah, I'm feeling good about it, actually (3/156/A)

> I said to my wife, I do feel like I've got a little bit more… va va voom (2/256/A)

> My gut in itself is more settled… which has quite a big impact to my day-to-day life (4/272/NT)

> I'm certainly now a bit more positive and more motivated to… get on with things (3/641/A)

The single dissonant view within this theme was contributed by a participant who experienced increased fatigue and muscle fatigue after changing diet. This was handled as an adverse reaction (see **6.8.3.ii** for a report of this). The participant attributed the reaction to the diet changes and noted a reduced sense of wellbeing (although they did also acknowledge improvements in general health and AF symptoms). This made NT less acceptable as a result:

> I was not looking forward to aspects of the therapy and, sadly, it lived up (down!!) to my expectations despite my trying really hard not to… give in to my preconception (4/142/NT).

Therapy experience: Participants discussed the experience of having their therapy, and whether this made it more or less acceptable to them. Acupuncture participants (n=11) were uniformly positive about their experience of the intervention, describing it variously as "exhilarating" (2/761/A), "interesting" (1/557/A), "inspiring" (2/256/A), "powerful" (2/163/A) and "thoroughly enjoyed it" (4/910/A). Eleven commented on experiencing the intervention as calming or relaxing, making it highly acceptable: "Very calming" (1/661/A); "I find it really relaxing" (2/163/A); "It seemed to calm me down a lot, and I was very… chilled and relaxed" (2/761/A); "It acted as a weekly oasis of relaxation" (4/910/A).

Six Acupuncture participants discussed the sensations of their therapy, which included "a real twinge… real strong stuff" (2/761/A) and "needles [that] hurt…" (3/156/A) although none perceived these as significant negatives affecting acceptability. Sensations could also be positive: one participant experienced "colours that appeared once the needles had been placed and wonderful lights… you feel suspended and euphoric" (1/661/A), while another felt "[a] fireball… a sudden release of sensation through the whole of my hand… it didn't feel painful… just an amazing sensation of sudden release" (3/641/A).

The dominant acceptability motif for the NT group was the enjoyment of learning about nutrition. Eight of the total nine NT participants said they had enjoyed "finding things that could help me have a healthier lifestyle" (4/840/NT), "learning about new foods to eat" (3/806/NT) or "learning more about nutrition + its affects [sic] on your body" (2/481/NT); "I enjoyed the learning aspects" (4/385/NT). One participant was introduced to "interesting" techniques that illustrated the link between AF and their diet:

> The daily calendar and the score-card… I can see there are such clear patterns of when I eat, what I eat and how strong my AF is and when it occurs and how long it lasts. There are some aberrations in there, but I would say probably between 80 and 90% is coloured by food (4/272/NT)

Participants in the NT group expressed a lower acceptability of intervention than the Acupuncture group for various reasons relating to the experience of therapy, including "having to eat and drink things I really don't like" (4/142/NT); the expense of diet changes (4/272/NT); and the work involved in rethinking meal plans for a household (4/272/NT): "Short-term it seemed to have a big difference, but there was an awful lot of work, time, effort, cost, on a day-to-day basis." One participant found the NT consultations too lengthy and infrequent, suggesting instead "more frequent online consultations to motivate but make them shorter" (1/464/NT).

Six participants (five Acupuncture, one NT) experienced the consultation process itself as therapeutic, seeing it as a chance to talk about themselves and receive attention and engagement:

> It's not often that you have the opportunity to express out loud how you're feeling about your own health… she would run through a whole set of checks of, how's this this week, how's that this week. And last week we talked about this – is this any better?… [it was] cathartic (4/910/A)

> She listened so well to how I felt about things, and worked very hard to try and ameliorate any problems and deal with them (4/142/NT)

Practitioners discussed self-care/lifestyle advice with participants, following up on implementation at successive appointments and adjusting advice where necessary. All participants receiving this advice experienced their practitioner as supportive during the change process: "she was very supportive and enthusiastic about my experiences" (3/806/NT); "always helpful and willing to listen" (4/113/A).

Participants across both groups felt the self-care/lifestyle advice received from their practitioner was often information they already knew, describing it as "somebody else telling you what you know you ought to do" (2/163/A), or "stuff that I generally knew that I shouldn't do" (4/385/NT). Two participants had tried various strategies in the past but welcomed support to reintroduce these (4/910/A, 3/806//NT). Two participants found advice would have been easier to follow with more free time (3/641/A, 4/910/A), while another would have liked "a little bit more about nutrition… earlier in the sessions" (4/113/A). A NT participant identified following self-care/lifestyle advice as their least liked aspect of study participation because "I had difficulty in motivation" (1/464/NT); by comparison, an Acupuncture participant identified lifestyle advice as a key reason for acceptability: "I learnt a lot about diet and fitness" (3/978/A), and another found it acceptable because "having tasks to do between sessions helped focus" (1/856/A). Self-care/lifestyle advice was generally more acceptable when it was "easy to understand and act on" (3/806/NT) or when "I liked the things she talked about and they weren't alien to me" (4/385/NT).

Six participants (five Acupuncture, one NT) found their therapy sufficiently acceptable as to declare an intention of continuing with appointments after the end of the study.

Practitioner relationship: This was an important element in the acceptability of the intervention. Participants had a uniformly high regard for their practitioner, irrespective of group. Acupuncturists were described as "attentive" (4/910/A), "gentle" (1/661/A), "calm" (2/761/A) and "a nice lady" (3/156/A), while nutritional therapists were seen as "approachable" (4/272/NT), "supportive" (4/142/NT) and "motivating" (4/385/NT). In the NT group, two participants identified the working relationship as important, specifically in relation to their acceptance and adherence to lifestyle advice and dietary plans:

> It was a bit like having done your homework… because of our relationship, I didn't want to say, no I haven't done that (4/385/NT)

> She was always trying to suggest, she was pushing me to go a little bit further, but very gently, very nicely done… in a way that you felt, yes, I will try and do that. She was extremely motivating, I thought, in the way she dealt with things (4/142/NT)

Similarly, three Acupuncture participants identified their working relationship as important for the acceptability of their intervention:

> It always helps, doesn't it? If you… feel comfortable with people… if I didn't feel comfortable, I probably wouldn't have gone, I'd have just stopped (2/163/A)

> The human relationships are extremely important – if you don't sort of enjoy the practitioner and they suddenly stick a needle in you and you don't particularly like them, I think that would be disastrous [laughs] and I probably would not have continued with it (1/661/A)

One dissonant view was expressed under the Practitioner relationship theme by an Acupuncture participant who felt their practitioner had not explained enough about the therapy for them to understand it, which left them feeling disengaged:

> I think that understanding… why [needles] were put where they were, and what they were doing, maybe would have made it feel like… I'm being included a bit more in what's going on (1/557/A)

Despite this, the participant felt they had a good working relationship with their practitioner: "she was lovely… it was a nice relationship" (1/557/A).

Logistics: Twelve participants commented on issues such as the process of booking their intervention appointments and making time for appointments. One of these identified this as their least liked aspect of study participation: "I have a hectic calender [sic]" (4/693/NT).

Appointment-related logistics were less acceptable to Acupuncture participants, who had a series of eight appointments and associated travelling time. Six Acupuncture participants praised the flexibility of their practitioner in accommodating their schedules:

> [We] narrowed it down [to a] programme of eight which could be accommodated by both parties… I thought at first it was going to be too difficult to do, but we did… that's a credit to [practitioner] (4/910/A)

This participant identified the process of booking appointments as the most disliked aspect of study participation. Another Acupuncture participant booked annual leave to meet their own preference for maintaining their appointments on a regular day and time (2/163/A); and three others felt the pressure of fitting appointments into a working schedule:

> It was a little bit awkward at times because I had to cancel stuff and move stuff … so there was a bit of pressure there in moving stuff around (2/761/A)

The time taken for travelling, and the stress of dealing with traffic, were a significant concern in the Acupuncture group, one of whom identified travelling as their most disliked aspect of study participation: "Some appointments were at a busy time of day on the roads" (4/113/A). Travel difficulties were also a significant issue for those participants travelling longer distances (up to 21 miles) to the acupuncturists' premises:

> I got there dead on time one day… when you get back of a tractor going at 20 mile an hour… it takes you an hour and a bit because our roads aren't the best for passing on (3/156/A)

Effect of COVID-19: Acupuncturists followed the COVID-secure guideline set out by the British Acupuncture Council (2022b). Participants found the COVID-19 precautions taken at the acupuncturists' premises, and the conduct of the acupuncturists themselves, reassuring:

> [I had] no worries at all, it was very well organised, very clean (1/661/A)

> She wore a mask… we both did a test… and she's constantly doing her hands with soap… I had no anxiety about it at all (2/761/A)

> She wears a mask all the time… there's gels… everything's clean in the room… and the doors are locked, you can't just come in… it's a one-way system around the building… so yeah, it felt quite safe (3/156/A)

> Not worried… precautions were good (4/910/A)

Nutritional therapy (NT) practitioners used video-calling software to hold consultations, email to encourage adherence and give supporting information, and online forms to collect information such as diet diaries. There was a mixed response to online working for the NT appointments: two participants found this their least liked aspect of study participation overall: "Would prefer face to face" (2/481/NT); "It's much nicer to be face to face" (4/385/NT), although for the latter this was balanced by the convenience of being online:

> Doing it online is much easier in that you don't have to [travel]. And it's quicker… what was, you know, the two or three hour session would have been a three or four hour session at least (4/385/NT)

NT participants were, in general, "used to" video-conferencing software and did not find it problematic (4/142/NT, 4/272/NT, 4/693/NT), although one participant had bandwidth issues during their online consultations, which made them less acceptable: "synchronisation of the speech was out so we would often find we were talking over each other a little bit" (4/385/NT). There is a possibility that participant 2/122/NT withdrew due to challenges with technology, although this was not confirmed by the participant.

Overall acceptability: 18 participants discussed the acceptability of their intervention as a whole. In the Acupuncture group, seven participants could not identify anything unacceptable ("nothing I particularly disliked" (4/113/A); "nothing to report" (2/256/A); "all very positive" (1/856/A)), while three others identified minor issues ("minor bruising" (1/661/A); "sometimes the needles hurt a bit" (2/761/A)) that did not affect acceptability.

For NT participants (n=9), the least liked aspects included less tractable items including the food they had been asked to eat, the length of time before the intervention showed any effects, online consultations and "eating offal" (4/385/NT); three could not identify any aspect they had disliked. One NT participant articulated a significant difference between the approach of NT and conventional medical care in terms of the location of therapeutic responsibility, and related this to the acceptability of NT:

> You have a medical issue, you go to your doctor, they write you a script, or they chop a bit off, and they fix it… you're almost giving responsibility over to them. Whereas [NT] is quite a change and it makes you think about yourself… it makes you do it yourself, in a way. And that's… a big commitment curve… You've got to want to do it long-term, really. And I think that's a decision you have to make yourself (4/272/NT)

6.4.3 Objective 4c: Effect of the pandemic on acceptability of interventions

COVID-19-related feasibility was not treated as a separate objective. Results for this domain are incorporated within domain 4b above.

6.4.4 Synthesis of objective 4: Acceptability of interventions

The joint display table synthesising the quantitative and qualitative data for objective 4 (**Figure 12**) is framed at individual participant level; it contextualises the quantitative acceptability rating given by each participant alongside a representative sample of their qualitative comments. Dissonant responses are therefore those that appear to diverge (in either direction) from the participant's

overall rating of acceptability. The table was organised by group to reveal any differences between groups, and additionally shows the quantitative analysis of average acceptability per group.

Objective 4: Acceptability of intervention – Joint display table

Group A (acupuncture) | Average acceptability rating = 1.5 (lower score = greater acceptability)

Participant	Qualitative comments	Acceptability rating*
1/557/A	[Somewhat improved] Knee pain/joints, sleep Feeling more relaxed Would like to have been more informed about what the procedure was aimed at treating [Side-effects] Mild dizziness after 1-2 sessions, eased in time	2
1/661/A	Immediately after each session a great feeling of uphoria [sic] and then slept very well. This also built up over the weeks. A good feeling... I may continue... as I believe in the long-term it may have reset my sinus. [Least liked] The insertion and removal of needles [Side-effects] A few bruises, very minor	1
1/856/A	[Very improved] Skin General well being. So relaxing. Helped relieve any tension. Nice surroundings/music. It should be available on prescription! Seriously considering future sessions. Definite improvement in the everyday flutterings of my AF. [Side-effects] None	1
2/163/A	[Somewhat improved] Bad back Acupuncture has helped my blood pressure to come down. [Most liked] The treatment helped me to relax and calmed my symptoms down. [Side-effects] None	2
2/256/A	[Somewhat improved] Sleep, Energy Felt better about myself. [Acupuncturist] was very helpful at every step/change. [Most liked] Had some deep sleeps following the treatments. [Side-effects] None	2
2/761/A	[Somewhat improved] Palpitations, Irregular heartbeat [Most liked] Meeting my accupuncturist [sic]. Care + Attention from that. I trusted her and felt she had great knowledge. I was in good hands. [Side-effects] None	2
3/156/A	[Somewhat improved] Mental attitude, Sleep [Most liked] Someone to talk to. Someone to support me [Least liked] Occasionally the needles hurt but [acupuncturist] repositioned them [Side-effects] On two occasions after the treatment I did'nt [sic] feel well for a day or so.	2

Group B (nutritional therapy) | Average acceptability rating = 2.1 (lower score = greater acceptability)

Acceptability rating*	Qualitative comments	Participant
1	[Most liked] Informative advice regarding specific food groups to avoid and food supplements to be aware of [Self-care advice not easy to act on] I needed to be more organised. For example required to do exercise first thing in the morning before eating [Side-effects] Nil	1/464/NT
2	Given me more knowledge of food and what to eat. Made me more aware of what to eat + when. [Most liked] Learning more about nutrition + its affects [sic] on your body. [Least liked] Zoom meetings. Would prefer face to face.	2/481/NT
3	[Somewhat improved] Dizziness, Palpitations, Light-headedness. Not as many episodes of symptoms. [Most liked] The explanations as to why the changes/certain foods are good for you. The suggestions about certain foodstuffs to eat more & what to reduce/cut out. [Side-effects] No	2/964/NT
2	[Extremely improved] Knee condition [Somewhat improved] Breathlessness [Most liked] Learning about new foods to eat, re-acquainting myself with food I had fell out of eating. [Least liked] Nothing [Side-effects] No	3/806/NT
5	Reduced sense of wellbeing... I have had to be very determined to stick closely to the recommended diet. [Most liked] Moving onto increased fruit – especially stewed apples and using Epsom Salts in my baths. [Least liked] Drinking a cider vinegar shot before meals! Eating food that looked awful. [Side-effects] I became extremely tired early on... [the diet] has not been wholly successful	4/142/NT
3	[Very improved] Bowel irregularity. Some weight loss To do the [therapy] well takes a lot of time and initial costs... Short term is doable long terms some of the restrictions will be hard to maintain [Side-effects] My bank balance – cost of ingredients	4/272/NT
1	[Very improved] Weight, Energy Generally feel in better health! [Most liked] Gaining nutritional knowledge [Least liked] Eating offal (purely on a voluntary basis to try it!!)	4/385/NT

** Rating on a scale of 1–7; low score = greater acceptability*

= consonant (with quantitative score) feeling, belief or opinion; = dissonant (with quantitative score) feeling, belief or opinion

Objective 4: Acceptability of intervention – Joint display table (continued)

Group A (acupuncture) | Average acceptability rating = 1.5 (lower score = greater acceptability)

Participant	Qualitative comments	Acceptability rating*
3/641/A	[Very improved] Parkinson's tremor This was a new proceedure to me and I found it thoughly benifical [sic] [Most liked] The routine and having to relax for 1 hour a week [Side-effects] No	1
3/978/A	[About the same] Heart, Leg, Shoulder Most liked] Relaxing and educational [Least liked] No comments [Side-effects] No	1
4/113/A	I feel calmer as a result of the treatment... I looked forward to my sessions. [Most liked] Being able to lie in a calm environment with no stress [Least liked] Some appointments were at a busy time of day on the roads. [Side-effects] No	2
4/910/A	[Somewhat improved] Sciatica. [Feel] calmer. I very much looked forward to my sessions as I enjoyed them. [Most liked] It acted as a weekly oasis of relaxation... opportunity to communicate freely about my wellbeing. [Least liked] Nothing really [Side-effects] Tired + lethargic after 1st session only.	1

Group B (nutritional therapy) | Average acceptability rating = 2.1 (lower score = greater acceptability)

Acceptability rating*	Qualitative comments	Participant
1	Small weight loss. As I was trying to go low carb diet already, the therapy helped me go further. [Most liked] Understanding carb/sugar more [Least liked] Nothing [Side-effects] None	4/693/NT
1	I feel a bit healthier with the exercise [Most liked] I enjoyed ways of finding things that could help me have a healthier lifestyle [Least liked] Nothing [Side-effects] No	4/840/NT

** Rating on a scale of 1–7; low score = greater acceptability*

= consonant (with quantitative score) feeling, belief or opinion; = dissonant (with quantitative score) feeling, belief or opinion

Figure 12: Objective 4 synthesis – acceptability of intervention

6.4.5 Assessment of feasibility for objective 4

This objective used two criteria to assess feasibility: participants' report of their satisfaction with group allocation, and of the overall acceptability of the intervention.

6.4.5.i Participant report of allocation satisfaction

This criterion assessed the percentage of randomised participants reporting high allocation satisfaction, with a feasibility threshold of 75% reporting ≥7 on a 10-point scale (10 = greatest satisfaction). As shown in **Figure 10**, 21 of 28 participants (75.0%) rated their allocation satisfaction within this range. By this threshold, objective 4a can be judged feasible.

6.4.5.ii Participant report of acceptability of intervention

This criterion assessed the percentage of participants reporting acceptability of the intervention at 1–3 on a 7-point scale (1 = most acceptable), with a feasibility threshold of ≥75%. As shown in **Figure 11**, 19 of 20 participants (95.0%) rated acceptability of their intervention within this range. By this threshold, objective 4b can be judged feasible.

6.5 Objective 5: Assessment acceptability

This objective focuses on participant assessments, which were carried out at baseline and a single follow-up approximately three months after baseline or at the end of treatment, whichever was later. This domain was answered using qualitative and quantitative data derived from questionnaires and interviews at both assessment points.

6.5.1 Objective 5a: Completeness of data returned for main outcomes

Completeness of data returned for the main outcomes was analysed as a proxy for assessment acceptability. Data missing due to participant withdrawal was accounted for (included) in this analysis.

The main outcome measures were:

- **EQ-5D-5L** (EuroQol Group, 2021). A complete dataset for the EQ-5D comprised six items;
- **Atrial Fibrillation Effect on Quality of Life scale (AFEQT)** (Spertus et al., 2011). A complete dataset for AFEQT comprised 28 items;
- **CardioSTAT® 7-day ECG monitor** (Icentia Incorporated, 2022). A complete dataset for the CardioSTAT® comprised a full seven-day recording (with or without noise);

- **Symptom diary** (**Appendix C**). No absolute measure of completeness was possible: entries were dependent on the participant firstly experiencing and secondly recording an AF episode in the diary. Symptom diaries recording episodes of AF were checked to ascertain the completeness of each episode's entry; a complete dataset for each episode entry comprised seven items. Four intentionally blank symptom diaries were returned at baseline (1/464/NT, 2/761/A, 3/684/A, 3/978/A) and four at follow-up (1/464/NT, 2/256/A, 3/684/A, 4/840/NT). These were recorded as 100% complete, i.e., the participant was not aware of any symptoms during the seven-day period.

Figure 13 shows each measure's percentage completeness at baseline and follow-up.

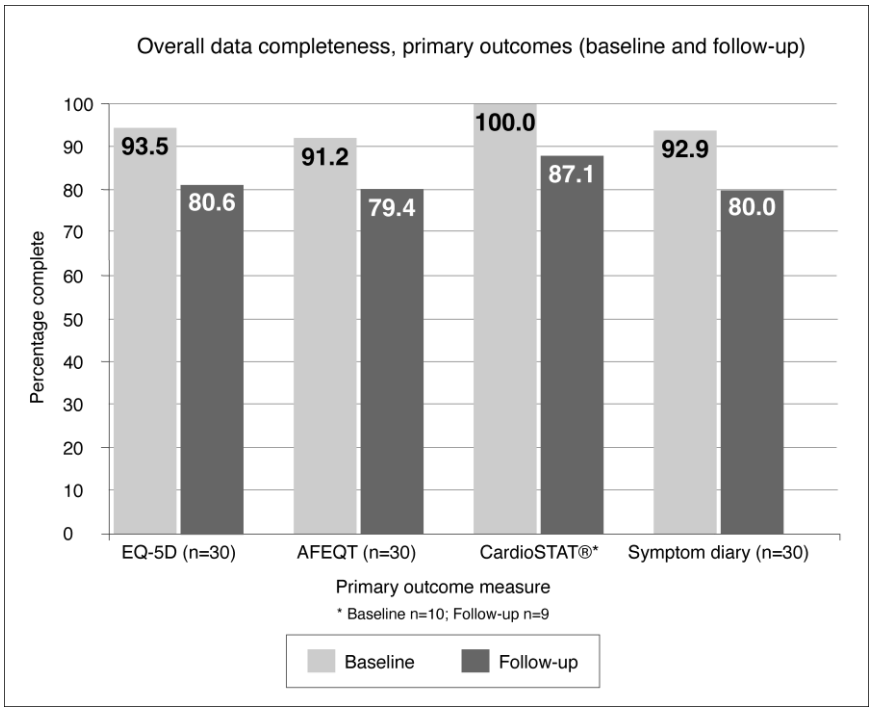

Figure 13: Data completeness for each main outcome at baseline and follow-up

Table 30 (overleaf) shows the aggregate completeness of all four measures at each measurement point, also taking account of data that was not collected due to participant withdrawal.

Table 30: Aggregate completeness of the four main outcome measures

	Overall completeness % (SD)*
Aggregate completeness, baseline	94.4 (3.9)
Aggregate completeness, follow-up	85.7 (7.4)
Aggregate completeness, overall	90.0 (7.2)

Analysis includes the data missing due to participant withdrawal

*n=30 for EQ-5D, AFEQT and symptom diary; n=10 for CardioSTAT®

6.5.2 Objective 5b: Acceptability of study assessments

6.5.2.i Quantitative analysis of assessment acceptability

A single measurement of both assessments' acceptability was sought in the follow-up questionnaire, in which n=25 participants were asked to indicate overall acceptability on a scale of 1–7 (1 = extremely acceptable). Results are shown in **Figure 14**. Note that a comparison of qualitative with quantitative data suggests that one of the two participants finding assessments "very unacceptable" (2/163/A) appears to have misunderstood the question scale, as this participant recorded a qualitative comment of "Nothing [disliked in the assessments] all good".

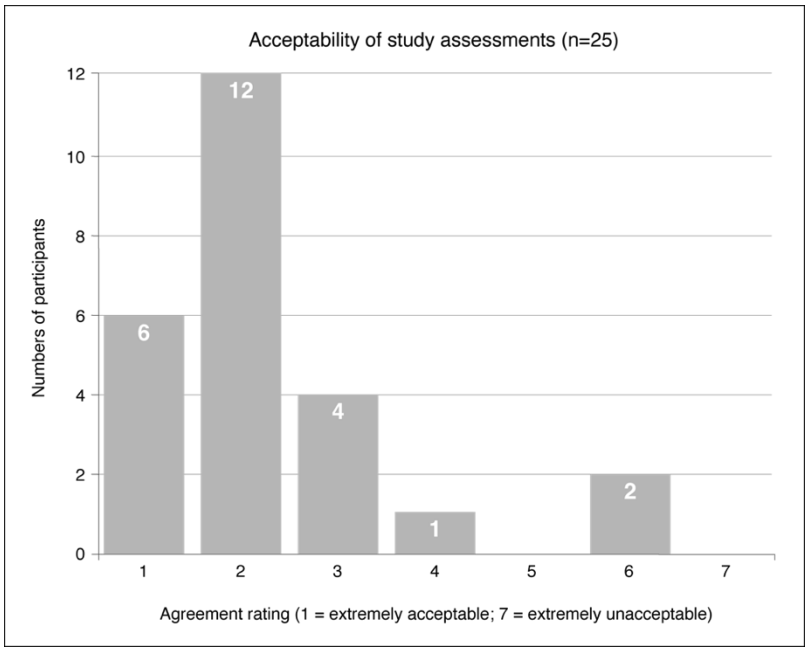

Figure 14: Overall acceptability of both assessments

To give a more detailed view of acceptability, in the baseline and follow-up questionnaires participants were asked to indicate aspects of the assessments they most disliked; results are shown in **Table 31**. Fourteen participants (48.3%) at baseline and eight (32.0%) at follow-up noted that there was no aspect of assessments that they disliked and therefore these participants did not identify a "most disliked" aspect.

Table 31: Most disliked aspects of assessments (baseline and follow-up)

	n (%) of 29 participants disliking this aspect most (baseline)	n (%) of 25 participants disliking this aspect most (follow-up)
Taking own measurements/weighing myself	6 (20.7)	2 (8.0)
Checking own blood pressure	3 (10.3)	3 (12.0)
Having medications noted	0 (0.0)	0 (0.0)
Fitting the CardioSTAT® heart monitor*	0 (0.0)*	2 (22.2)*
Completing the questionnaire	1 (3.4)	5 (20.0)
Finding a quiet, private place to do the assessment	2 (6.9)	0 (0.0)
Using video-calling technology to do the assessment	1 (3.4)	1 (4.0)
Doing the assessment online rather than in person	0 (0.0)	4 (16.0)
Taking delivery/collection of study equipment	0 (0.0)	0 (0.0)

* n=10 participants at baseline, n=9 participants at follow-up

6.5.2.ii Qualitative analysis of assessment acceptability

Qualitative data was collected from 30 interviews and 54 questionnaires (baseline and follow-up), and analysed using reflexive thematic analysis. This yielded four feasibility-related themes: **Specific elements**; **Working online**; **Post-assessment commitments**; and **Overall acceptability**.

Specific elements: Under this theme, participants commented on the acceptability of **Questionnaires**, **Interviews**, **Taking own measurements**, **CardioSTAT® monitor** and **Symptom diary**.

Questionnaires attracted comment from nine participants, who found them in general too long: "Reduce the questions involved" (1/557/A); "Less paperwork" (4/272/NT); "Too many questions" (4/693/NT); "I am fairly slow at filling in forms" (4/840/NT); "I'm not very competent in filling out forms" (3/156/A). Participant 1/884/UC said they were "used to paperwork" but felt others may have difficulty:

> I can see for some people there's a lot there and they may say… this is too much for me. I know if my mother was given [the questionnaire], she'd be… oh there's far too many questions, oh why do they wanna know that… (1/884/UC)

Participants expressed preferences for doing the questionnaire in two separate sessions (1/884/UC), or having the questions read to them and the answers completed by the researcher (4/910/A). The latter participant also gave the single dissonant view under this theme, saying they had "genuinely enjoyed doing it. Because it gave me this opportunity to articulate a few of the things that have been going on with me that normally are never explored" (4/910/A).

Under **Interviews**, three participants identified that the interviews were a positive experience:

> Obviously these things can be therapeutic and being able to talk about them, so that's… definitely a positive thing (2/515/UC)
>
> I'm talking to you, you're giving me attention, you're giving me *care*… and you know, it all adds up, it really does… the attention is fantastic (3/761/A)
>
> Your interviews… haven't been inconvenient, they're not a great duration, and you know, a pleasant experience just talking about what I've experienced and what you're trying to get out of us (3/641/A)

Participants **took their own measurements**. For 12 participants, the business of taking their own anthropometric measurements was disliked: "a bit tricky using the tape measure" (4/113/A); "tricky" (2/515/UC); "difficult when… having headphones on & wearing a dressing gown" (1/557/A); "it's just finicky" (4/910/A). Some participants were neutral: "I'm a [healthcare professional]… doesn't bother me" (4/272/NT); "standing on the scales and measuring my hips and so on is not an issue" (4/385/NT).

Undressing to take measurements was disliked by two participants who found their environment cold (1/856/A, 1/661/A). One participant found it difficult to find a private place to do the assessments (2/964/NT), while another disliked undressing due to "body shame" (1/884/UC). Participants were offered the opportunity to turn off their cameras while taking measurements but all chose to leave cameras on, with four expressing a preference for this because (typically) "[I'm] not sure I'll be able to turn it back on again" (3/156/A). While participants generally did not name privacy or dignity issues as problematic, the researcher noted that nine participants (baseline) and eight (follow-up) took anthropometric measurements out of camera view; when asked about this, participants gave a range of reasons including preferring different rooms for warmth or household privacy reasons (3/806/NT, 1/856/A, 4/693/NT, 2/481/NT, 2/964/NT); the difficulty of using the weighing scales on a carpeted floor (4/840/NT, 1/557/A, 2/256/A, 2/639/UC); and generally finding it easier not to be observed (2/256/A, 3/978/A). Although the researcher made every effort to brief the participants before their exit from screen/sound, inevitably some measurements may not be accurate as correct procedures may not have been followed (for instance, ensuring that the tape measure was located correctly and not twisted, or weight was measured while wearing minimal clothing).

Three participants had an aversion to taking their own blood pressure (2/136/UC, 3/684/A, 3/806/NT), while three others felt uncomfortable that their blood pressure was higher than expected (3/156/A, 4/142/NT, 4/272/NT). Participant 4/910/A said they would "prefer to come to a centre and have that information taken by somebody who's suitably trained", despite the COVID-19 risk, and one other participant agreed: "perhaps if someone did the measuring" (3/684/A). One dissonant perspective came from a participant who found the measurements "fun" (2/761/A).

The **CardioSTAT® monitor** was found to be acceptable: "I found it] really easy to wear and after a while you forget you've got it on" (4/385/NT); "I was able to forget it was attached to me. It was comfortable enough to forget about during day and night" (2/761/A); "You felt it for the first day or so then you… just got used to wearing it" (1/884/UC). One participant compared this with the Holter monitor they had worn during diagnosis "which was quite a pain really, [so] it would be difficult to complain about something that's so wearable" (2/515/UC). Balancing general acceptability, two participants felt anxious about showering with the monitor (explicitly permitted with this monitor and reiterated to participants at each fitting) (4/385/NT, 2/256/A), one experienced anxiety having accidentally disconnected a lead while asleep (4/910/A), and one had problems with residual adhesive after removing the electrodes (1/661/A).

Completing the **Symptom diary** over a seven-day period following each assessment was generally acceptable, with participants commenting "fine" or "no problem" regarding its use (1/557/A, 2/256/A, 2/515/UC, 2/639/UC, 4/142/NT). Two participants expressed a wish for more space to describe symptoms (4/142/NT, 2/515/UC), while three found it difficult to complete due to having "nothing really to report" (2/256/A, 1/557/A, 1/884/UC). Two participants who were also wearing the CardioSTAT® monitor discussed the possibility that they were less diligent about completing the diary due to wearing the monitor, with differing points of view:

> I added some notes that [the symptom diary] wasn't necessarily asking for, so I did take it quite seriously (2/515/UC)

> Well, this machine does it all, why do I need the diary? (1/884/UC)

Under the **Working online** theme, nine participants stated a preference for in-person working: "[online is] impersonall [sic]" (3/684/A); "the human contact is always beneficial" (3/641/A); "[better to see] the assessor in person" (4/113/A); "rather speak face to face" (2/481/NT); "maybe [better] in person" (2/174/NT); "always better face to face" (4/385/NT). Four of these balanced this preference with an understanding of the circumstances: "…that's COVID for you" (1/557/A) or an appreciation that working online avoided travelling:

> If I came to an appointment, it would probably, when you take into consideration the travel time to and from, it would probably be just as long for me (4/910/A)

> Online is… fine as [I] didn't have any travelling time (2/964/NT)

A dissonant view came from a participant who found it problematic to leave their home, and so expressed a preference for online assessments:

> I don't have to book the time out, travel somewhere else… the kit arrives on my door, and I'm used to doing it online, like this. So it's easy (4/272/NT)

Only one participant described themselves as "not used to technology" (2/481/NT). The researcher observed that only one assessment was troubled by bandwidth issues that rendered communication more than passingly difficult (1/557/A, follow-up).

Participants were also agreeable to having a case of measuring equipment ("that box of tricks" (4/385/NT); "your box of toys" (1/661/A)) delivered up to an hour ahead of each assessment, and having it collected again afterwards. One participant found it a "rigmarole" and, while understanding the COVID-19 imperative, expressed a preference to attend a study centre:

> That's the way it has to be for a very good reason. But it would have been so much easier… if it could be streamlined… where you just make an appointment to see people and [we] may be through this in an hour flat (4/910/A)

Ten participants gave short verdicts on the **Overall acceptability** of their assessments. Even those who had singled out specific problems expressed a high level of acceptability: "All very easy. Well explained + easy to follow" (1/856/A); "quite enjoyable… interesting… nothing that's unpleasant about it" (2/639/UC); "nothing I didn't like" (4/272/NT); "all fine" (2/515/UC); "they've been fine" (3/156/A); "I liked all aspects of my assessment" (2/761/A). One compared the assessments favourably with hospital visits: "having gone through all the treatments I've had in hospital and things… you know, it's nothing" (2/639/UC). Four admitted to some inconvenience in scheduling and giving up time for assessments, but felt this was at an acceptable level (1/884/UC, 2/256/A, 3/156/A, 4/693/NT); one participant had a dissonant point of view, finding the assessments time-consuming and suggesting instead "feedback on a monthly basis" (1/464/NT).

6.5.2.iii Exploratory analysis: Researcher observations on online assessments

The researcher observed some effects on feasibility arising from the need to hold assessments online during the COVID-19 pandemic.

The first of these was the requirement to deliver and collect measuring equipment to participants' homes. This was time-consuming, particularly when assessing participants living further from the study centre (10 participants lived 10–21 miles distant); the researcher offered evening and weekend appointments in addition to working hours but capacity issues slowed the rate at which participants could be assessed. This extended the enrolment period (defined as the time from

received consent form to baseline assessment, average 31±19.9 days, n=29 participants) and the follow-up period (end of intervention to follow-up assessment, average 17±12.1 days, n=25 participants). Significant extra travel costs were also incurred in delivering/collecting measuring equipment, and the requirement for robust broadband facilities while the researcher was working from home during the pandemic posed further feasibility challenges in terms of logistics and costs.

The researcher also observed that, for some participants, issues of ethics and authenticity were raised by assessments being held online. Three participants had partners present for both assessments (2/163/A, 2/256/A and 4/385/NT), while one had a partner present at baseline (2/174/NT). During interviews, partners sometimes gave answers on behalf of the participant, occasionally without the participant's invitation to do so. The researcher was careful to check that the participant agreed with the answer given in every case, but it is not possible to know whether the presence of the partner prohibited disagreement, nor what answers might have been given had the partner not been present. Participants also occasionally consulted partners regarding some questionnaire answers. Latent coding practice (Byrne, 2022) was applied with particular care to these interviews and questionnaires, along with reflexive memos that allowed the researcher to explore different meanings and carefully consider the interpretation of answers given in these circumstances.

Finally, self-fitting the CardioSTAT® ECG monitors may have been partly responsible for the higher-than-expected proportion of non-analysable data retrieved from some participants' monitors (see **Table 33** below for this data). Despite the researcher's verbal explanations and the use of an upper-body model to demonstrate, some participants found it difficult to locate the necessary anatomical features required for positioning the monitor; while the researcher carried out a visual check on the positioning of all monitors on screen, this may not have been adequate to detect sub-optimal location. It was also not possible to check the adherence of electrodes to the skin during fitting; poor adherence may have contributed to noise.

The average length of assessments varied depending on the allocation of participants to subgroups for CardioSTAT® and interview. Average durations are shown in **Table 32**.

Table 32: Average duration of assessment components

Assessment components	Average duration* (hh:mm)
Complete questionnaire (n=54)	00:28
Complete interview (n=30)	00:30
Fit CardioSTAT (n=19)	00:19
Take measurements (n=54)	00:24

n = total number of observations pooled from baseline and follow-up * durations averaged between baseline and follow-up

6.5.3 Objective 5c: Effect of the pandemic on the acceptability of assessments

COVID-19-related feasibility was not treated as a separate objective. Results for this domain are incorporated within domain 5b above.

6.5.4 Synthesis of objective 5: Acceptability of study assessments

The joint display table (**Figure 15**, overleaf) was used to synthesise quantitative and qualitative data. Quantitative data represents participants' most disliked aspects of assessments, and is shown alongside consonant, or dissonant, themes in the corresponding qualitative data.

Objective 5: Acceptability of assessments – Joint display table

QUANTITATIVE		QUALITATIVE	
Baseline Assessment as a whole	0* →	← 0†	I think everything's been absolutely fine…I'm very happy to continue to do [assessments]. (3/641/A) All fine really, did not mind (2/515/UC) The process was… considerably less arduous than I had expected (4/142/NT)
Follow-up Assessment as a whole	3 ↑	↓ 0	All very easy. Well explained + easy to follow (1/856/A) ALL WAS good (2/761/A)
Both Assessments as a whole	1 →	← 1	I honestly can't think of anything that's difficult to take, that I would say is negative about the whole thing (4/272/NT) Time-consuming… would prefer feedback on a monthly basis (1/464/NT)
Taking own measurements/weighing myself or Difficulties in taking my own measurements	9 ↓	↑ 10	Found it a bit tricky using the tape measure (4/113/A) Just the fiddle of it (4/910/A) It was fun… When you showed me where to measure and the ratio between hips and your waist… it was interesting to learn such things. (2/761/A)
Checking my blood pressure	6 →	← 6	Just personal (dislike). I have issues taking blood pressure too much (2/136/A) Blood pressure really high… painful when cuff was blowing up (3/156/A)
Fitting the CardioSTAT® heart monitor**	3 ↑	↓ 1	I find it a bit difficult because of my neck, to actually look down and see what I'm doing (4/385/NT)
Completing the questionnaire	6 ↓	↑ 9	It lastid [sic] the longest…too many questions (4/693/NT) Long winded way of getting the information (4/272/NT) Gave me this opportunity to articulate a few of the things that have been going on with me that normally are never explored (4/910/A)
Finding a quiet, private place to do the assessment	2 ↑	↓ 1	Difficult to find a private place at home where not disturbed (2/964/NT)
Using video-calling technology to do the assessment	2 ↑	↓ 1	This type of mechanism for face to face meetings… I'm used to software to do these (1/884/UC) I've got things like a laptop, used them for a long long time, quite happy with that (4/142/NT) Not used to technology (2/481/NT)
Doing the assessment online rather than in person	4 ↓	↑ 9†	[Better to do] it face-to-face & in person (1/557/UC) Capturing full information about participent [sic] is more possible in person (4/910/A) Online is also fine as didn't have any travelling time (2/964/NT)
Other: Room very cold!	0 ↓	↑ 2†	Room very cold! First time done online assessment – will know better for next time! (1/856/A) It was cold [when we did the baseline assessment] so probably did need my dressing gown [1/661/A]

Number of participants between baseline and follow-up has been aggregated (n=29 baseline, n=25 follow-up)
** n of 54 participants noting this as the most disliked aspect of the assessments*
† n of 54 of participants who disliked this at interview, or in free-text questions in questionnaires or other documents (baseline and follow-up)
*** n=10 participants at baseline, n=9 participants at follow-up*
= consonant feeling, belief or opinion; = dissonant feeling, belief or opinion

Figure 15: Objective 5 synthesis – acceptability of assessments

6.5.5 Assessment of feasibility for objective 5

This objective used two criteria to assess feasibility thresholds.

6.5.5.i Completeness of data returned for main outcome measures

This criterion assessed the completeness of data provided by participants for the four main outcome measures, and had a feasibility threshold of ≥80% completeness. **Table 30** shows data as 90.0% ± 7.2% complete. By this threshold, this domain can be judged feasible.

6.5.5.ii Participants' report of acceptability of assessments

This criterion focused on participants' quantitative report of assessment acceptability, with a feasibility threshold of ≥90% of participants reporting a score of 1–3 on a 7-point scale (1 = extremely acceptable). As shown in **Figure 14**, 22 of 25 (88%) of participants scored the assessments overall at 1–3. On this basis, this aspect of Santé-AF was not judged feasible; however, the failure to meet the threshold was due to a probable misunderstanding of the question scale by a single participant, and when corrected for this error, it is reasonable to consider this threshold to have been met.

6.6 Objective 6: Utility of CardioSTAT® monitor

Santé-AF used a two-lead ambulatory ECG monitor, the CardioSTAT®, manufactured by Icentia Incorporated (2022), worn by a third of all participants (n=10) over a seven-day period at baseline and follow-up to detect active AF. The cost of each monitor, including its associated data analysis services, was £150+VAT, reduced from a standard £200+VAT as a goodwill gesture by the manufacturer. This objective focused on the utility of the monitor, where "utility" was defined as the CardioSTAT®'s role in the feasibility of a future trial. This objective is divided into three domains.

6.6.1 Objective 6a: Agreement between symptom diaries and CardioSTAT® data

All participants were asked to keep a seven-day symptom diary at baseline and follow-up. For the 10 participants who also wore a CardioSTAT® monitor (n=9 at follow-up), the data from the monitor was compared with the symptom diary, expressed as the number of minutes of AF/symptoms recorded by each method.

Table 33 (overleaf) shows data extracted from the CardioSTAT® and the symptom diaries. Participant datasets from baseline and follow-up have been paired for ease of reading, but for the purposes of comparison they were not differentiated; baseline data for participant 2/174/NT, who was lost to follow-up, is also included. Columns in grey show the percentage of active AF recorded by the CardioSTAT® compared with the percentage of perceived symptoms recorded in the symptom diary.

Table 33: Active AF and perceived symptoms, per participant

	CardioSTAT® data			Symptom diary data				
	% non-analysable	Active AF (minutes)**	AF % of analysable data	# entries	# entries corresponding to AF	# entries corresponding to non-analysable	Perceived symptoms (minutes)	Symptom % of 7-day recording period
1/661/A baseline*	18.9	8,197.6	100.0	10	8	2	572.7	5.7
1/661/A follow-up	24.4	6,475.1	100.0	5	2	0	690.0	8.1
1/884/UC baseline*	8.5	0.0	0.0	3	0	0	114.6	1.1
1/884/UC follow-up	4.0	9,937.0	100.0	6	6	0	5.0	0.0
2/174/NT baseline	4.9	0.0	0.0	5	0	0	75.0	0.7
2/256/A baseline	83.0	1,720.2	100.0	1	0	1	5.0	0.0
2/256/A follow-up	86.4	1,181.7	100.0	0	0	0	0.0	0.0
2/481/NT baseline	55.1	4,705.5	100.0	4	1	3	90.0	0.9
2/481/NT follow-up	17.4	8,399.6	100.0	2	2	0	35.0	0.3
2/515/UC baseline	18.3	285.0	2.8	3	2	0	150.0	1.5
2/515/UC follow-up*	56.7	112.6	1.1	8	2	0	305.5	3.0
2/761/A baseline	1.0	10,287.1	100.0	0	0	0	0.0	0.0
2/761/A follow-up	4.6	9,800.4	100.0	2	2	0	480.0	4.7
2/964/NT baseline	9.5	661.4	6.5	7	2	2	49.6	0.5
2/964/NT follow-up	7.2	235.5	2.3	6	2	4	41.0	0.4
4/385/NT baseline	6.4	0.0	0.0	4	0	0	165.0	1.6
4/385/NT follow-up	2.6	0.0	0.0	1	0	0	0.2	0.0
4/910/A baseline	5.8	9,734.6	100.0	5	5	0	125.0	1.2
4/910/A follow-up	3.9	10,168.3	100.0	1	0	1	10.0	0.1

* Some or all durations missing from symptom diary. Mean of all other observations used to impute missing values.

** Taken from analysable data only

To understand **Table 33**, it is necessary to describe some features of the CardioSTAT®:

- **Measurement of active AF:** The CardioSTAT® is designed to detect active AF during a seven-day period, but data does not give the timing or duration of individual episodes. Instead, active AF is represented as a percentage of the total minutes of analysable data during the seven-day period.
- **Analysable data:** The CardioSTAT® has been shown to have excellent agreement with the standard method of AF detection (the 12-lead ECG Holter monitor) in terms of AF presence (Kappa = 0.99, SE=0.01, 95%CI = 0.97–1.00) (Nault et al., 2019). However, like all ambulatory ECGs its signal is subject to noise generated by poor electrode contact with the skin, muscle noise, or accidental disconnection of the monitor from the electrodes over the course of the seven-day period; this obscures the ECG data (tagged as "non-analysable"). Therefore the number of minutes of AF recorded by each CardioSTAT® does not represent the number of minutes of AF experienced by the participant *over the course of seven days*, but rather the number of minutes of AF experienced by the participant *over the duration of analysable data*, i.e., an arbitrary period defined by the extent of noise. While the CardioSTAT® monitor is therefore a useful means to detect the *presence* of AF, it cannot detect the *extent* of AF as an absolute figure relative to the seven-day wear period.
- **Verification of symptom diary entries against CardioSTAT®:** Some symptom diary entries cannot be verified as either concurrent or non-concurrent with AF, because they correspond to periods of noise in the CardioSTAT® data (e.g. 1/661/A baseline, 2/964/NT follow-up).

Bearing these features in mind, the principal finding shown in **Table 33** is the wide discrepancy – notwithstanding the different lengths of recording time – between the percentage of perceived symptomatic time self-reported in the symptom diary and the percentage of actual AF as recorded by the CardioSTAT®. It can also be seen that some participants gave a nil report of symptoms in the symptom diary compared with a positive CardioSTAT® reading – i.e., they did not feel symptoms where AF was present (e.g. 1/884/UC follow-up; 2/256/A follow-up; 2/761/A baseline). Similarly, some participants gave a positive self-report of symptoms in the symptom diary compared with a nil CardioSTAT® reading – i.e., they felt symptoms where AF did not exist (e.g. 1/884/UC baseline; 2/174/NT baseline; 4/385/NT baseline).

Table 33 also shows that some participants appeared to be in constant AF throughout the analysable data period. While the analysable data period in all cases is less than the seven-day wear period, this is suggestive of AF progression from paroxysmal to persistent (i.e., a duration longer than seven days (National Institute for Health and Care Excellence, 2021)).

A progression threshold had been set for this objective based on the association between AF recorded by the CardioSTAT® and the symptoms recorded in the symptom diary. Unfortunately the arbitrary recording period meant that the analysis and therefore application of this threshold was not possible; however, it was clear that the symptom diary recorded far less symptomaticity than the active AF recorded by the monitor.

Researcher notes of informal chat during follow-up assessments (not formally analysed as it was not part of interviews or questionnaires), suggested that as many as 15 participants may have returned diaries that were somewhat inaccurate due to emotional responses to symptoms, questionnaire fatigue, not having the diary to hand, or simply forgetting. Additionally, some participants may have been aware of symptoms but actively disregarded them. For instance, participant 2/761/A returned an intentionally blank symptom diary at baseline, having not felt any symptoms during the seven-day period (although their CardioSTAT® recorded 100% AF during analysable data); however, after an informal conversation about the diary during the follow-up assessment the participant recorded 480 symptomatic minutes in the symptom diary at follow-up (again corresponding to 100% AF during analysable CardioSTAT® data).

The symptom diaries of participants who wore a CardioSTAT® monitor may have been particularly unreliable because participants may have relied on the monitor rather than recording symptoms in the diary (despite a clearly worded request during assessments to regard the two as independent). The case of 1/884/UC is illustrative: at baseline the participant recorded 1.1% symptoms (114.6 minutes) in the symptom diary when in fact sinus rhythm persisted throughout the analysable data period; at follow-up, they recorded 0.0% symptoms (5.0 minutes) in the diary despite the CardioSTAT® recording 100.0% AF throughout the analysable data period. At interview, this participant revealed their awareness that they were in AF during follow-up but felt "this machine does it all, why do I need the diary?".

6.6.2 AF between and within participants

Another interesting feature of **Table 33** is the heterogeneity of AF severity (as recorded by CardioSTAT®) between participants at baseline. This can be seen in the comparison of two participants (2/515/UC and 2/964/NT) with the remainder of the cohort, most of whom had a far greater percentage of active AF during the baseline analysable data period (most frequently 100.0%) than these two participants (2.8% and 6.5% of the analysable data period respectively).

Within-participant variations can also be observed longitudinally in **Table 33**: at baseline, participant 1/884/UC was in normal sinus rhythm throughout the analysable data period, but at follow-up recorded 100.0% AF. Adding to this (not shown in **Table 33**), a fourth participant (1/661/A) was aware of being normal sinus rhythm at pre-randomisation stage, but by the time of baseline

assessment (≈60 days later) the participant recorded 100% AF, which persisted at follow-up. This level of within-participant variation (0-100%) may reflect the AF characteristics of a specific cohort in a single-centre study, but may also be indicative of characteristics in a wider population.

6.6.3 Objective 6b: Influence of CardioSTAT® on participation and retention

In the baseline questionnaire, all participants were asked whether the CardioSTAT® had influenced their decision to participate; at follow-up, the n=9 participants wearing the monitor were asked whether it had been influential in their decision to remain in the study. The results are shown in **Table 34**. The monitor was somewhat influential in participation, and remained somewhat influential in retention.

Table 34: Influence of CardioSTAT® on participation and retention

	n (%) participants citing this reason	n (%) participants citing this as most important reason
Reasons for participation (baseline): Wanted the chance to have AF monitored by CardioSTAT® (n=29)*	7 (24.1)	3 (10.3)
Reasons for retention (follow-up): Wanted to continue to have AF monitored by CardioSTAT® (n=9)*	4 (44.4)	1 (11.1)

* n at baseline = all participants; n at follow-up = all retained participants wearing CardioSTAT®

Separately, CardioSTAT® wearers (n=9) were asked at follow-up to indicate how strongly the monitor had influenced their decision to participate, on a scale of 1–5 (where 1 indicated strongest influence). One participant (11.1%) gave a rating of 1; the remaining eight gave a rating of 3 (neither influential nor non-influential).

6.6.4 Exploratory analysis: CardioSTAT® experience

A descriptive analysis was carried out to examine more closely participants' experience of the CardioSTAT® monitor, using data collected in the follow-up questionnaire (n=9 participants) (**Figure 16**, overleaf).

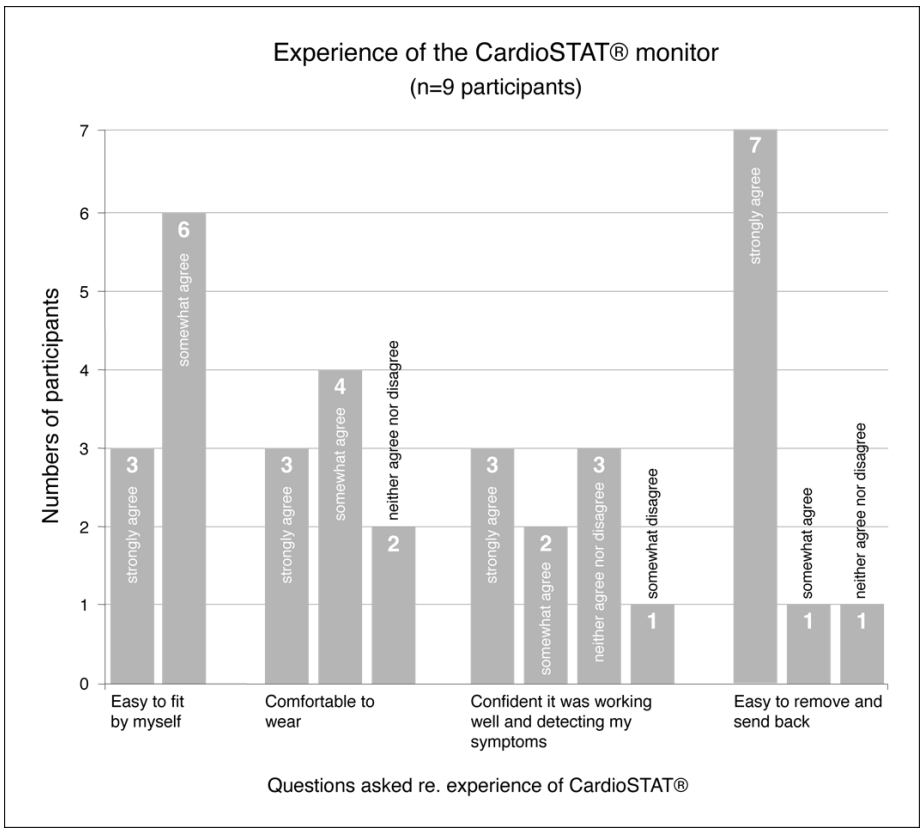

Figure 16: Participants' experience of the CardioSTAT® ECG monitor

6.6.5 Objective 6c: Effect of the pandemic on utility of CardioSTAT® monitor

COVID-19-related feasibility was not treated as a separate objective. Results for this domain are incorporated within domain 6a, and the exploratory analysis of CardioSTAT® experience.

6.6.6 Assessment of feasibility for objective 6

This objective had two progression thresholds. The first concerned participants' report of the CardioSTAT®'s influence on their decision to participate, and to remain in the study. This was set at a feasibility threshold of ≥50% of CardioSTAT® users reporting 1–2 on a 5-point scale (where 1 = most influential). As shown in **Table 34**, only one (11.1%) of the actual monitor users reported it as strongly or somewhat influential on a decision to participate (1–2 on the 3-point scale). By this threshold, this objective of Santé-AF cannot be judged feasible; however, it was judged inappropriate to apply a progression threshold to this objective, which was more exploratory than deterministic. This feasibility domain was accepted as inappropriate and the progression threshold was not applied.

Due to the nature of the CardioSTAT® data described above, the second progression threshold could not be applied.

6.7 Objective 7: Overall experience of study participation

This objective is divided into two domains focused on participants' and practitioners' overall experience of study participation. Specific aspects of participants' experience have been analysed under other objectives, including objective 4 and objective 5. This section focuses on overall experience.

6.7.1 Objective 7a: Participants' overall experience of study participation

This domain was answered using quantitative and qualitative data.

6.7.1.i Quantitative analysis of overall acceptability of study participation

A single measurement of the acceptability of overall study participation was sought in the follow-up questionnaire, in which n=25 participants were asked to indicate overall acceptability on a scale of 1–7 (where 1 represented "extremely acceptable"). The results are displayed in **Figure 17**. Note that the outlier finding study participation "extremely unacceptable" appears to have been a misunderstanding of the question scale, as the participant contributed the comment "Very interesting and helpful, I believe it has helped me and my symptoms"; this participant also continued privately with the intervention at study end.

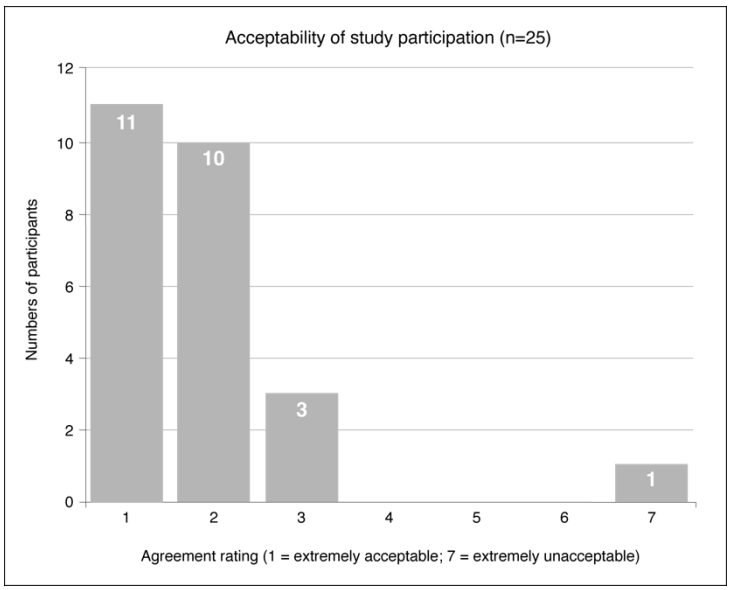

Figure 17: Acceptability of study participation overall (n=25 participants)

For a more detailed view of overall study participation acceptability, questionnaires asked participants to indicate the most disliked element of study participation (once at baseline, once at follow-up). The results are shown in **Table 35**.

Table 35: Most disliked aspects of study participation

	n (%)* of participants disliking this aspect most
Hearing about group placement (n=29)	5 (17.2)
Reading the participant information pack (n=29)	5 (17.2)
Completing the permission-to-approach form (n=29)	2 (6.9)
Doing the screening call (n=29)	2 (6.9)
Reading the permission-to-approach information/forms (n=29)	1 (3.4)
Completing the consent form (n=29)	1 (3.4)
The overall length of time to begin the trial (n=29)	1 (3.4)
Contacting practitioner to make first appointment (n=20)	1 (5.0)
Travelling to/from acupuncture appointments (n=11)	1 (9.1)
Having NT consultations online (not in person) (n=9)	1 (11.1)
Following self-care advice (n=19)	1 (5.3)
Other: Making time for therapy appointments (n=19)	1 (5.3)
Other: Sometimes the needles hurt (n=11)	1 (9.1)
Receiving the queries phone call (n=29)	0 (0.0)
Making an appointment for the baseline assessment (n=29)	0 (0.0)
Replying to the SMS poll (n=29)	0 (0.0)
Having therapy (n=19)	0 (0.0)
Relationship with practitioner (n=19)	0 (0.0)

* % calculated using applicable n noted in row

To understand participants' attitudes to COVID-19 risk during participation, and whether this had affected experience of study participation, quantitative data was collected via baseline and follow-up questionnaires regarding participants' level of worry regarding risk. Risk was indicated on a three-point scale (1 = extremely, 3 = not worried at all). The results are shown in **Figure 18** (overleaf).

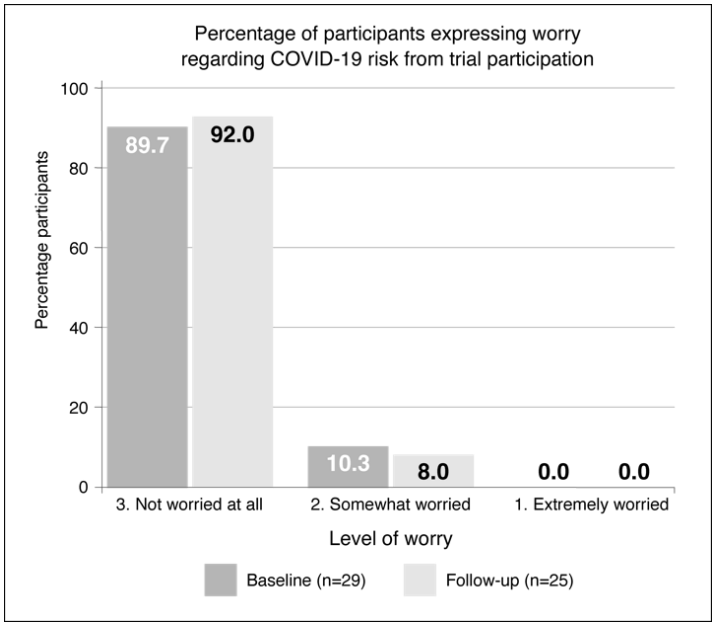

Figure 18: Percentage of participants expressing worry regarding COVID-19 risk

6.7.1.ii Qualitative analysis of participants' experience of study participation

Qualitative data from baseline and follow-up interviews, and answers to the questionnaires' free-text questions on the subject of participation experience, was analysed using reflexive thematic analysis. Where participants focused on specific aspects of either intervention or assessments, these have been analysed under the relevant objective; this section instead analyses general responses to study participation as a whole, including those aspects that are not analysed elsewhere.

Reflexive thematic analysis generated two themes: **Recruitment burdens** and **Overall experience of participation**.

Recruitment burdens: Fifteen participants across all groups expressed a general dislike of reading the study documentation, or completing the permission-to-approach form or the consent form. Participants described themselves as "not a good form filler" (4/910/A, 3/156/A), while two participants disliked "all the initialising" (4/227/UC) and "too many signitures [sic]" (4/693/NT) for the consent form in particular. The participant information pack was felt to be burdensome: "takes time" (1/464/NT); "there was a lot to read and digest" (2/481/NT); "lots of reading" (3/684/A); "there was a lot to go through" (4/113/A). 2/515/UC felt the study was low risk, making the informed consent documentation "unnecessarily large" and potentially a deterrent:

> Some people must get that and go wow, gosh, I don't know… well, do I really want to still go ahead with it, or do I really read all of that or do I scan it and just tick it (2/515/UC)

Dissonant perspectives on the participant information pack were contributed by three participants:

> I liked the pack and the pen, that cheered me up, and it was interesting getting a big pack through the post, I don't get much post these days (2/294/UC)
>
> The information pack that came through was very easy to read, and very interesting (4/385/NT)
>
> Incredibly impressed with all the documentation that came out… I thought it was very thorough, very helpful, very competently done, there wasn't stuff [just] for the sake of it, I thought it was all very useful (4/142/NT)

Two participants commented on the screening call, finding it overly long:

> I thought it was a bit long-winded and it seemed to go on forever… I thought oh, how many more questions (1/557/A)
>
> I thought… oh crikey, it just seemed to go on… it seemed very long-winded (1/661/A)

Overall experience of participation: Participants gave short, generally positive views of their experience: "very interesting and helpful" (2/163/A, 2/639/UC); "all new + interesting" (1/856/A); "interesting" (1/557/A); "intreeging [sic] + interesting at all stages" (2/761/A); "fine… not onerous at all" (2/964/NT); "very informative experience" (3/806/NT); "happy with everything" (3/978/A); "very enjoyable!" (4/385/NT); "enjoyed taking part" (4/693/NT); and "enjoyed doing the coarse [sic]" (4/840/NT).

There were no dissonant perspectives within this theme.

6.7.2 Objective 7b: Effect of the pandemic on participants' experience of participation

COVID-19-related feasibility was not treated as a separate objective. Results for this domain are incorporated within **6.4** and **6.5**. An assessment of COVID-19 effect on participants' overall experience of participation is incorporated in **6.7.1.ii**.

6.7.3 Objective 7c: Practitioners' experience of study participation

All six practitioners commented on their study participation experience in their exit interviews. Reflexive thematic analysis yielded five feasibility-related themes: **Working with participants**; **Admin**; **Support and training**; **COVID-19 pandemic**; and **Payments**.

Working with participants: Practitioners discussed issues affecting how they were able to deliver therapy to participants during the study. Participants randomised in a study were perceived to have a different engagement or "starting point" (P1/A) from practitioners' regular patients. NTs in

particular were aware of a different level of engagement at the outset that called for more effort on their part:

> There's a bit of a difference because normally the therapeutic relationship starts before you even see them… they've done some searching, they've found you, they've chosen you… and by the time you actually see them, that investment, that commitment, it's already started. When a client has not paid for NT, when a client has not chosen NT, then you don't get them as invested in it… I had to work quite hard to get that investment (P4/NT)

> Basically these are people who haven't specifically come to you, they haven't chosen you to be their practitioner… it's kind of been foisted upon them… so [participant] was sitting there, leaning back against the sofa, like "what can you do for me?"… I think trying to [get] buy-in was the hardest bit with some people (P5/NT)

> Maybe not as committed at the baseline as most of my clients… Maybe had they come to me by their own will, maybe they would have had more questions, maybe they would have talked a little bit more (P6/NT)

Despite engagement being perceived as tricky at the outset, all NTs felt they had achieved a productive working relationship with their participants by the end of their therapy:

> All of mine were prepared to do the work, they took it seriously, and one of them probably was so desperate that… it was like a last chance to do something about it. And so [they were] really motivated (P5/NT)

> They [became] really really open and you could see that they were curious about diet and stuff. Very rewarding… a really pleasant surprise (P6/NT)

By contrast, acupuncturists perceived less difference at the outset between study participants and their usual patients. While one practitioner sensed a trust in conventional medicine uncharacteristic of her usual patients ("most of my patients are often a bit pissed off with conventional medicine, and very happy to be stepping away" (P1/A)), all acupuncturists found their participants to be within a usual scope of personality type and engagement level:

> [3/156/A] was a challenge at the start because [they were] like, I'm a nurse and this is all rubbish… but I do get patients like that in normal practice, because they're the husbands of the wives that have been sent… it's not completely unusual to get someone that needs a little bit of proof or a bit of reassuring (P2/A)

> They were level with my average patient… different profession, different view of alternative therapy, different ownership of their health… being pushed into the treatment room by their family sometimes… yeah, I can level them with my own patients very nicely (P3/A)

Admin: Practitioners discussed their thoughts about the ways in which study administrative work differed from normal practice. Work included submitting professional documentation during study

set-up and regular invoicing for payments. This was seen as "just part of being on the trial" (P2/A) and "not too awful" (P6/NT). The most significant element of administrative work was the requirement to complete a log book for each participant (**Appendix A**, Practitioner documents section) in which practitioners were asked to give details of interventions from each appointment, and to express their thoughts about the participant's progress in an end-of-intervention summary. The log book followed a template; in view of the holistic nature of the therapies and/or the pragmatic trial requirement to follow routine practice they were occasionally experienced as inflexible and "frustrating" (P1/A):

> I'm looking at the whole person [so] suddenly I'm incorporating points that will also help with a sprained knee… there doesn't seem to be an opportunity to explain that it isn't a narrow focus on their AF this week (P1/A)

> There's a bit that says "what symptom does this refer to" and that was sometimes quite hard because [some advice] is for everything, an underpinning principle, so I can't say it's just for this or that… because we don't deal with symptoms, we deal with underlying causes (P4/NT)

Support and training: Practitioners discussed the training workshops and the support available to them, including WhatsApp groups, the study manual, the website and the peer supervision groups held during the intervention period.

Acupuncturists saw the training workshops as useful Continuing Professional Development (CPD), but NTs did not: "CPD is more like what I learn as fact about nutrition health… workshops weren't focused on that" (P6/NT).

WhatsApp groups (one for each therapy, plus one for all practitioners) were generally liked by all practitioners for the sense of community they promoted (P1/A, P2/A) and the swift responses they yielded (P4/NT). One practitioner liked the groups' way of being "helpful when I didn't know I had a problem… like with [cancellation], so when it happened to me I just handled it smoothly because I already saw the example on the group" (P3/A). Balancing this, the same practitioner felt uneasy when the acupuncturists' WhatsApp group became more social than study-focused: "I'm not a social media user, I feel anxiety" (P3/A). Two other practitioners took steps to avoid feeling "overly pinged" (P1/A): "if it was too much I just didn't reply… I can be bolshy like that" (P5/NT); "if I feel overwhelmed I just put it away… better just to keep it to business" (P6/NT). The researcher also felt the stress of being at least nominally responsible for a forum that, by its nature, could not be moderated, and strove to balance the tone of all groups between the banter felt by some practitioners to be "the best bit" (P2/A) and the strictly business/procedural focus preferred by others. The researcher sought post-hoc verbal permission at exit interviews to use some content from WhatsApp groups in study analyses.

The study manuals (**Appendix A**, Practitioner documents section) were seen as a useful resource, particularly in view of the five-month delay between the training workshops and the start of the intervention period. Practitioners "initially read it from cover to cover" (P1, P2/A) and revisited it during the initial stages of working with participants: "I looked at it again when I was first filling in the log book to make sure I was doing it right" (P5/NT); "a sort of double-check if I [had] understood things" (P6/NT). Two used it as a guide in the case of an uncontactable participant (P4/NT) and a potential adverse reaction (P5/NT).

The study had a public-facing website (www.sante-af.org) that included a secure area for practitioners only, used as a document repository. All practitioners liked the website and used it to download copies of documents including the manuals and log books.

A peer supervision group meeting was held for each therapy towards the end of the intervention period (3 April 2022 (acupuncturists) and 18 March 2022 (NTs)). These meetings were not part of the original study protocol and were offered to both groups in response to the intention, expressed by the acupuncturists on their WhatsApp group, to hold their own peer supervision session. The convening of a group for the specific purpose of discussing study issues and participant-focused therapeutic approaches may have presented challenges to study integrity, pragmatism and generalisability; peer supervision groups were therefore convened for each therapy under the (loose) moderation of the researcher. Attendance was optional and unpaid, but all practitioners attended their group meeting; acupuncturists met in person while NTs preferred to meet online. Meetings lasted for 105 minutes (acupuncturists) and 61 minutes (NTs). Discussions were regarded as confidential and non-judgemental, with a self-determined degree of personal and professional reflection; practitioners were required to preserve confidentiality of participants and practitioners, as in standard peer supervision practice (Rothwell et al., 2019). Topics discussed in both groups included the nature of working with study participants, and specific issues arising from study participation; acupuncturists in particular shared and critically discussed their therapeutic strategies and the TCM manifestations of participants' symptoms. To support practitioners in open disclosure and self-reflection, the groups' data was not included in analysis for this feasibility study; instead, the researcher noted themes and specific issues that were subsequently raised in practitioners' individual exit interviews. Practitioners uniformly felt they had benefited from the groups: "it was really interesting to see how similarly and also how differently we'd approached things" (P1/A); "you don't ever see anybody else, or you know, question what anyone else is doing, so I liked that" (P2/A); "nice that we were all in the same boat… definitely supportive" (P5/NT).

In general, practitioners did not feel their experience of trial participation was affected by the **COVID-19 pandemic**. However, the significant COVID-19-related delay between the training workshops (July 2021) and the start of the intervention delivery phase (December 2021) due to

participant recruitment delays caused by PICs' workload meant that some practitioners felt "rusty" (P6/NT) and needed to revisit trial procedures. This was done either via the study manual or workshop recordings available via the practitioner-only section of the trial website.

Under the theme of **Payments**, practitioners contributed thoughts on whether, and how, the payment of fees had influenced their experience of study participation. Practitioners explored the fact that study administrative work was indirectly recompensed via a small surplus added to the treatment fees; the surplus was judged adequate to cover administrative work.

Routine practice for acupuncturists is to charge a premium for the first appointment, because "there's a lot of work to do in the first session, it takes longer" (P1/A), whereas routine practice for NTs is to average a first-consultation premium across a package: "we do most of our work around the first appointment... but it evens out" (P4/NT). Unfortunately a premium for an individual appointment could not be accommodated under the CRN's funding structure. Acupuncturists were unperturbed by this in view of the surplus paid for treatments: "it evens out" (P2/A). NTs were also unperturbed, but their comments appeared more frequently in the context of reassurance gained from the fact that the study offered up to two payments for short-notice cancellations or no-show participants; as the NT course of consultations ran to three appointments, NTs knew they would be paid for all participants' appointments if participants attended the first consultation. This knowledge was important in the context of no available premium for the first appointment: "we knew the participant was committed to the three sessions… so it was more or less guaranteed that money would be there eventually" (P4/NT).

The financial implications of participants' attrition (or inability to attend for treatment) were generally viewed with equanimity by the practitioners (one acupuncturist and two NTs, each of whom saw three participants rather than the anticipated four): "it's OK… you did say you couldn't promise" (P6/NT). The acupuncturist admitted "obviously I had a moment of "oh, that's going to be a lot of money" because that was a quarter of it" (P2/A) but this practitioner and one other were "kind of relieved… I was still feeling a little bit of anxiety up to meeting each new [trial] person" (P2/A); and "relieved… I was so busy at that time" (P5/NT).

Some frustration was experienced as a result of the perceived tardiness of the University of York in paying invoices (practitioners put this at an average of six to eight weeks from submission of invoice) particularly by the acupuncturists, who were accustomed to being paid in advance or on the day of treatment delivery: "that was tricky" (P2/A). The same acupuncturist pointed out that because three study participants per week made up a quarter of her weekly workload, "that's quite a big hole in your cashflow" and felt that "maybe a little bit quicker would be awesome". By comparison, NTs, who were more used to invoicing clients and waiting for payment, took the delays

in their stride: "it's part of running a business" (P4/NT); "you can plan accordingly… if you are not used to that, it could be slightly demotivating" (P6/NT).

6.7.4 Objective 7d: Effect of the pandemic on practitioners' experience of study participation

COVID-19-related feasibility was not treated as a separate objective. Results for this domain are incorporated within domain 7c above.

6.7.5 Objective 7e: Practitioners' experience of intervention fidelity

This objective was added following publication of the extension to PRECIS-2 guidance on pragmatic trials, adapting it to feasibility studies (Chan et al., 2021). Feasibility in relation to intervention fidelity was assessed by a combination of the following analysis (data taken from practitioner exit interviews) and exception-based reports of scope-of-practice deviations (**6.8.1.i**).

No analysis of the delivered interventions was conducted, as it was not relevant to feasibility; for the purposes of judging fidelity and safety, reporting was by exception. It should also be noted that generalisability in relation to intervention fidelity relates only to a UK context; there may be differences in therapy and practice parameters between the UK and other countries.

Practitioners' views were sought on the scope of intervention they were required to deliver, as set out in each therapy's study manual (**Appendix A**, Practitioner documents section), and whether this could be delivered as intended. Reflexive thematic analysis of practitioners' comments resulted in four themes relating to feasibility: **Focus on AF**, **Self-care/lifestyle advice, COVID-19** and **Scope of therapy**, the last of which divided into five sub-themes: **Therapy restrictions**, **Referrals**, **Number of appointments**, **Frequency of appointments** and **Effects of study participation**.

Practitioners discussed an unexpected difficulty in knowing whether to **focus on AF** to meet the needs of the study. They had been clearly advised to follow their usual practice in treating the whole patient rather than simply aiming to treat participants' AF alone, but in practice this was not as simple as it appeared. For some practitioners, treating the whole person aligned with routine practice and met participants' broader needs:

> The concept of balancing means you can't just focus on one thing (P2/A)

> [I didn't feel constrained to focus on the AF]… especially because most of my participants weren't telling me "I get this many episodes a week", they were like "no, I'm fine, don't really notice it" (P4/NT)

> The only time was the one client who said that [AF] really affected her daily life… whereas for some of the others, they didn't even know they had it. So I was just working out what the things were that would help them the most" (P5/NT)

For others, usual practice involved more emphasis on the presenting condition:

> You've always got your main attention on the thing they've come with. Everybody's quite complex and there are things you can be distracted by, so you have to be careful about that distraction… no different to normal (P1/A)

One acupuncturist felt constrained to focus on the AF throughout treatment, despite her usual practice being different:

> At the start, I [am] consciously making decisions steering towards the AF, and it was not an issue at the beginning. Towards the later part, say session six onwards, the background issues stand out more and more… I thought about what in real practice I would do differently [which is that] I got rid of the *biao* [symptoms], [so now] I would go for the *ben* [root cause] (P3/A)

Self-care/lifestyle advice was generally considered by NTs to be an integral and accustomed part of their therapy, and no feasibility issues were found. Acupuncturists, for whom lifestyle advice was effectively an adjunct, varied their approach according to their judgement of what the participant needed. One acupuncturist gave plentiful advice to one participant, but felt a second would not heed it as "[their] lifestyle was pretty set", and "just stopped with [another] because [they] knew everything already" (P2/A). Another acupuncturist gave moderate self-care/lifestyle advice to all participants, according to their Chinese medicine diagnosis (P1/A). One acupuncturist gave very little self-care/lifestyle advice to any of her four participants, revealing her conviction that self-care/lifestyle advice was unhelpful or possibly counter-productive for most patients, and her usual scope of practice did not include such advice:

> "I'm very wary with lifestyle advice… [it's] common knowledge they can find on Google or the NHS website… I feel everybody wants to have a hand in giving advice. I just float myself into complete reverse." (P3/A).

COVID-19: Acupuncturists worked to a COVID-secure guideline (British Acupuncture Council, 2022a), while NTs delivered consultations online. Although both modifications represented substantial changes to pre-COVID ways of working, by the time intervention delivery began in December 2021 practitioners of both therapies were fully habituated to the changes. NTs had transitioned to online delivery following the first lockdown in March 2020, while acupuncturists had worked to various versions of the COVID-secure guideline since being permitted to re-open in July 2020. All practitioners commented that COVID-secure intervention delivery was "the new normal… it is how I work now" (P6/NT) and the trial's requirements represented "no change from how I normally work at the moment" (P2/A).

Under **Scope of therapy**, practitioners considered the **Therapy restrictions** placed on them by the study. These were generally not seen as problematic by the acupuncturists, whose restrictions were in any case part of the British Acupuncture Council's Guide to Safe Practice (British Acupuncture Council, 2018), particularly with regard to anticoagulated patients.

NTs were more significantly restricted, being prohibited from recommending supplements or commissioning functional or genomic testing. With the available toolkit limited to dietary strategies and lifestyle advice, NTs initially felt "not constrained… I'm not someone who does a lot of testing and supplements anyway" (P4/NT) or even, in two cases, "liberated" (P5/NT, P6/NT) from having to "do all that work with medications and interactions" (P5/NT). But as consultations went on, NTs felt the restriction of scope more, commenting that participants were not benefited by this:

> By the time I came to the third interview, I did begin to think that really and truly I was a bit stymied because this was the point where I would be thinking about supplements… for one or two I really thought that some tests [would be helpful]… (P5/NT)

Another practitioner found a "borderline ethical" issue in not being able to recommend a supplement to a participant:

> I really suspected that he must be very deficient in Vitamin D… from his dietary diary and also from some other symptoms… so it was sort of the hardest bit – borderline ethical, because it would have benefited him… (P6/NT)

For all practitioners on the study, **Referrals** to other forms of complementary therapy were prohibited to avoid participant burden and confounding factors. Practitioners noted the challenges posed by not being able to refer onwards. One practitioner wanted to suggest "some kind of CBT-type support" (P1/A) for a participant with anxiety about their AF and health in general, and three practitioners wanted to recommend a manipulation therapy for participants with soft-tissue problems (P1/A, P2/A, P5/NT). Three practitioners did not encounter the need to refer study participants at all.

Practitioners had varying views on the **Number of appointments** available:

> In terms of getting where we needed to get to, I felt that eight is pretty good… if you'd done 12… it would have been too much of a commitment, and if you'd done… four to six, it wouldn't have been enough to get to that point of confidently feeling better (P2/A)

Other practitioners did not feel this was sufficient to effect meaningful change:

> I wouldn't expect eight treatments to be done and dusted, but it would give us an indication if things were improving (P1/A)

> When somebody has a lot of issues and you start in at the beginning, it's not gonna suddenly clear up their AF in the two-month period… it's gonna take longer than that (P4/NT)

Limitation in the number of appointments was generally less problematic for the NTs, the nature of whose therapy aimed to "give people the tools [so] they can fly on their own" (P4/NT), creating "less of a hard ending" (P5/NT).

Practitioners reflected on the restrictions posed by the **Frequency of appointments**. Training workshops and the study manuals explicitly permitted the flexing of appointment frequency to meet participants' individual needs, and to enable practitioners to follow routine practice; despite this, all practitioners followed the encouraged patterns of once-weekly appointments for acupuncture and once-monthly appointments for NT, commenting that the intervention window (10 weeks for Acupuncture, 12 weeks for NT) offered insufficient scope for routine practice:

> I might say, try to do six weekly and then a two-weekly and then a two-weekly, if we're doing normal practice, just to give them confidence that that's how it works… that it does stay and hold… but not in the time we had (P2/A)

> I usually treat them three to five times… five to six maximum if it doesn't go well. Then if good, I would dilute to fortnightly. If… the symptoms get a lot worse, by day eight or nine, then OK, sorry, come back to once a week. I think it's a luxury to see them consecutively for eight weeks (P3/A)

> The way I work, usually people don't need to come back in four weeks' time. They often run with it, and we see how it goes over several months before they come back. So [with one participant]… we tried to delay his third appointment because… he needed to carry on doing what he was doing. If he'd been paying for his consultations it would have been a waste to have another consultation [at that point] (P4/NT)

A dissonant perspective here was contributed by P6/NT, who felt that both the number and the timing of consultations was "just right": "there are exceptions, but [three consultations at monthly intervals] [is] what I do in my practice normally".

Under **Effects of study participation**, practitioners talked about the ways in which they were aware that taking part in the study had changed their routine practice. Two practitioners were apprehensive about submitting their log books to the study centre, feeling that these would be "judged" (P2/A, P5/NT); another practitioner described a feeling that the researcher was "in the room" while study treatments were being delivered (P3/A). The clearest effect of study participation was seen in the absence of therapy explanations given to participant 1/557/A by practitioner P3/A, which left the participant feeling "[not] included… in what's going on" (1/557/A); by P3/A's own admission, omitting explanations was not part of her usual working practice, and resulted from an

awareness of delivering treatments for a study: "I did not want [to] change course of trial by saying the wrong thing" (P3/A).

The fact that all acupuncturists worked from the same clinic premises may have led to some contamination regarding the effects of study participation between practitioners. One practitioner described an incident in which she discussed with a second practitioner the extent to which the second practitioner was discussing with her participants what could be expected from treatment (part of routine practice). The second practitioner had refrained from all discussions about treatment expectation, due to her feeling that this may have influenced the participants' outcomes (although this was in direct contradiction of advice given in the training workshops). The first practitioner then adopted the second practitioner's practice with her own participants, and passed this to the third practitioner, although the third chose to continue discussing treatment expectation with her participants.

6.7.5.i Scheduling of first appointments

There was an average delay of 41.1 days±16.9 days between participant notification of allocation and first appointment. Participants' baseline assessments were carried out before allocation was notified, and there was a minimum 10 days' delay between baseline assessment and notification (seven days for data collection using the symptom diary and CardioSTAT® monitor followed by an average three days to return these to the study centre, with allocation notified immediately on receipt). Adjusting for this 10-day period, approximately 31.1 days of delay was due to other factors. Acupuncture appointments were subject to longer delays (37.1 days±15.3 days) compared with NTs (24.6 days±16.9 days).

Reasons for the delay were explored with all practitioners and participants in the intervention groups during interviews. Reasons given included participant delays in contacting practitioners, participant availability, practitioner availability, availability of suitable appointment days/times, and the winter holiday 2021/22. Practitioners generally did not find the delays unusual: "there's often a bit of time before I can fit somebody in… more so if they've only got some days they can come" (P1/A); "I normally have a waiting list… I freed up more times for trial people so I could get to them faster" (P5/NT). Most participants took the delay in their stride.

6.7.6 Synthesis of objective 7: Participants' experience of study participation

The joint display table (**Figure 19**, overleaf) synthesises qualitative and quantitative data for participants' overall experience of study participation (i.e., not including practitioners). Quantitative data is a collation of participants' most disliked aspects of study participation, and the overall rating

of participation acceptability; these are shown alongside consonant or dissonant themes in the corresponding qualitative data.

Objective 7: Experience of study participation – Joint display table

QUANTITATIVE		QUALITATIVE	
Reading the Permission to Approach information (n=29)	1* →	← 1†	The information is required. Hard to improve (2/256/A)
Completing the Permission to Approach form (n=29)	2* →	← 2	Not a good form filler (4/910/A) [Would have been better to] compile some questions together (4/693/NT)
Reading the Participant Information Pack (n=29)	5* ↓	↑ 6	There is a lot to read and digest (2/481/NT) [Better with] not quite so much reading material (4/113/A) I quite liked the pack and the pen, that cheered me up (2/294/UC)
Completing the Consent Form (n=29)	1* ↓	↑ 2	All the initialising (4/227/UC) Too many signitures [sic] (4/693/NT)
Doing the Screening Phonecall (n=29)	2* →	← 2	I thought oh, how many more questions (1/557/A) It just seemed to go on... I thought it seemed very long-winded (1/661/A)
The overall length of time taken to begin the study (n=29)	1* ↓	↑ 2	I'd just like to get on with it, and you know, get on, finish it, do it (1/661/A) I'd have liked to get going sooner... if I'm going to do it, I want to get on with it (4/272/NT)
General experience of participation – extremely, very or somewhat acceptable (n=25)	24• ↑	↓ 11	Very interesting and helpful (2/163/A, 2/639/UC) Intreeging [sic] + interesting at all stages (2/761/A) Very informative experience (3/806/NT) Happy with everything (3/978/A)
Professionalism of study and personnel (n=25)	0 ↓	↑ 8	Both [researcher] and [acupuncturist] have been very professional from start to finish (2/256/A) I think it's been impressive in terms of... being professionally sort of put together (2/515/UC)
Reading the Winter newsletter (n=13)	0 ↓	↑ 1	Getting that newsletter was a real boost... I think it's been really well done (4/385/NT)

** n of participants noting this as the most disliked aspect of the study (of total n noted in row)*
• quantitative data from questionnaires
† n of participants who commented on this at interview, or in free-text questions in questionnaires or other documents (baseline and follow-up)
= consonant feeling, belief or opinion; = dissonant feeling, belief or opinion

Figure 19: Participants' experience of study participation

6.7.7 Assessment of feasibility for objective 7

No precedents could be identified to guide a feasibility threshold for the overall acceptability of study participation. The threshold was set at 75% of all participants rating acceptability 1–3 on a 7-point scale (1 = extremely acceptable). As can be seen in **Figure 17**, 24 of 25 (96.0%) of participants rated overall acceptability of participation at 1–3 on the 7-point scale. By this criterion, the overall acceptability of participation in Santé-AF can be judged feasible.

6.8 General study findings

This section contains results that were not covered by the study's feasibility objectives, but were identified as being of interest in the planning of a future large-scale trial.

6.8.1 Protocol deviations

The original study protocol was amended with approval by the NHS London/Surrey REC in May 2021 (version 1.5) (NHS Health Research Authority, 2021a). Deviations from version 1.5 are noted here.

6.8.1.i Deviations from the specified scope of practice for interventions

Space was provided in the log book for practitioners to note deviations from the specified scope of practice. No deviations were noted, but one deviation emerged during the practitioners' exit interviews as it became apparent that one practitioner (P3/A) gave very little lifestyle advice to participants.

6.8.1.ii Intervention duration

The period within which the series of eight acupuncture treatments could be taken was shortened from 12 weeks to 10 weeks, to keep overall trial timelines concise following delays in trial start.

6.8.1.iii Extra dietary plan

An extra dietary plan was provided to participant 4/142/NT to mitigate an adverse reaction.

6.8.2 Findings from the ethics approval process

The PRECIS-2 pragmatic trial assessment tool (Loudon et al., 2015) was modified by Chan et al. (2021) for pragmatic trial feasibility studies, and includes a recommendation to investigate potential issues with ethical approval if the future trial's consent procedures are waived or otherwise altered for pragmatic trial contexts. The process of informed consent in Santé-AF was not altered from a traditional full informed consent process, but a brief account of the ethical approval process is provided here to support a future trial.

The initial application was submitted for approval to the London Surrey REC via the IRAS system on 20th March 2020. The REC returned a provisional outcome on 29th April 2020 (NHS Health Research Authority, 2020b), requiring clarification of the following points:

1. Study outcomes;
2. Safety of diet recommendations in the context of anticoagulants;
3. Safety of electroacupuncture in the context of AF;

4. Request to use the CHA_2DS_2VASC and HAS-BLED tools as eligibility criteria;
5. Whether adverse event risk quoted in protocol relates to AF patients only;
6. Wording change to inclusion criterion: "patients with paroxysmal AF who can detect when they experience AF"
7. Change of wording biased towards acupuncture and NT;
8. Inclusion of material in PIS on risks of: (i) effect of existing medication (anticoagulants) may be affected by changing diet or taking supplements; (ii) acupuncture causing bleeding;
9. Clarification in PIS of what is being measured;
10. Clarification in protocol that caffeine reduces risk of AF;
11. Study's consultant cardiologist to approve all responses.

Responses were submitted on 15th May 2020.

The REC sent a "Response incomplete" response on 16th June 2020 (NHS Health Research Authority, 2020c), requiring more information on the following points:

12. Clarification of the study hypotheses regarding the associations between AF, symptoms, and quality of life;
13. Further changes to the PIS eligibility criteria regarding perceptible paroxysmal AF of at least once-weekly frequency;
14. Further changes to biased wording in the PIS regarding acupuncture and NT;
15. Further information regarding the effect of diet changes on the effect of anticoagulants;
16. The inclusion of figures and types of adverse events relating to acupuncture in the PIS;
17. The inclusion of a statement in the PIS to make it clear that continuation of treatment after the end of the study would be at the participant's own expense.

Responses were submitted on 26th June 2020. There were no further queries. The REC subsequently provided a favourable opinion on 3rd November 2020 (32 weeks from submission to receipt of approval). For all documents, see **Appendix A**, Protocol and ethics section.

Changes were made where appropriate, but some requested changes were either not valid or not relevant (e.g., 2, 4, 8(i), 10, 12, 15) and were therefore not made, with rationale for this provided to the REC. The REC appeared also to misunderstand the nature and level of risk associated with both interventions, with the result that the required amendments to the PIS amplified the representation of risk. Finally, it is not clear why there was such a significant delay between the submission of the second response and receipt of approval (18 weeks); the researcher sent several follow-up emails between August and October, but these received no response.

The proceedings of HRA RECs are not available for scrutiny by applicants, so it is not possible to understand the reasons for the duration of the process or the high number of invalid or irrelevant requests for change.

Four Amendments (substantial and non-substantial) were subsequently approved. See **Appendix A**, Protocol and ethics section for details.

6.8.3 Findings regarding safety of interventions

To provide evidence of the safety of both interventions, safety data was collected.

6.8.3.i Practitioner report of safety data

Practitioners were asked to note serious adverse events, adverse reactions or adverse events unconnected with study treatment, in log books. No serious adverse events or unconnected adverse events were reported; nine adverse reactions were reported, shown in **Table 36**.

Table 36: Practitioner reports of adverse events from log books

Practitioner / participant	Description	Classification	Duration	Reported at appt. number	Corroborated by participant self-report?
P2/A					
2/163/A	Median nerve sensation while needling lower forearm	Adverse reaction	Transient	7	No
3/156/A	Slight headache during needling	Adverse reaction	Transient	2	Yes
P3/A					
1/557/A	More tired than usual	Adverse reaction	Previous week	2	Yes
1/557/A	More tired than usual	Adverse reaction	Previous week	3	Yes
1/557/A	More tired than usual	Adverse reaction	Previous week	4	Yes
1/661/A	Mild bruising on lower forearm	Adverse reaction	Previous week	2	Yes
1/661/A	Mild bruising on left upper chest	Adverse reaction	Previous week	3	Yes
3/641/A	Bruising on left lower forearm and left 11th rib	Adverse reaction	Previous week	3	No
P5/NT					
4/142/NT	Muscle fatigue and tiredness worsening over 4 weeks	Adverse reaction	4 weeks	2	Yes

6.8.3.ii Adverse reaction of participant 4/142/NT

The adverse reaction of 4/142/NT was reported by the practitioner to the researcher, who in turn reported to the academic supervisors and the Trial Steering Committee (TSC), which handled the incident by correspondence (**Appendix A**, Trial Steering Committee section). The TSC's consultant cardiologist gave his opinion, based on the participant's medical history, that the participant's lipid-regulating medication (Pravastatin) was the likely cause, perhaps exacerbated by unaccustomed exertion, but the participant's GP (routinely consulted by the participant during this period) disagreed but gave no reasons for this. The participant completed a current four-day diet diary which was scrutinised by the TSC's expert NT member, who concluded:

> Overall, I would consider that the chances of his symptoms being related to his diet to be infinitesimally small. As mentioned previously, the medication is the likely culprit… my judgement would be that he should feel better as a result of his diet, not worse.

A revised dietary plan was formulated by the participant's NT (P5/NT) and checked by the expert NT; this aimed to improve digestion and absorption of nutrients from food, and to reduce muscle fatigue while maintaining gains in sleep quality and reductions in dyspnoea. The extra dietary plan represented a minor protocol deviation for the study, but a response to newly arising symptoms was within the scope of routine practice for NT and was ethically required. The TSC felt that if the participant was happy to continue in the study and able to withdraw at any time, they were satisfied with the safety of this decision. Academic supervisors advised that the incident did not require further or expedited reporting (i.e., to the HRA or the NHS REC), although it was included in governance reporting and the final HRA report.

The participant chose to continue in the study. During the follow-up assessment, they shared with the researcher their own thoughts on the cause of the adverse reaction:

> [P5/NT] was trying to move my cells from using sugar-based things for energy to fat-based. And my body, after 70 years of sugar-based energy [changing] in four weeks, was not coping with the change (4/142/NT)

6.8.3.iii Participant report of negative effects of intervention

To provide triangulation for practitioner reports, participants were asked about undesired or negative effects of their intervention ("side-effects") in the follow-up questionnaire. Minor side-effects were most common in the Acupuncture group, in which three participants reported "wooziness" or being "spaced out" after treatment (1/557/A, 1/661/A, 2/163/A); one reported minor bruising (1/661/A); another a slight headache and, separately, not feeling well "for a day or so" (3/156/A); and another "tired + lethargic after 1st session only" (4/910/A). One participant noted the side-effect of "my bank balance – cost of ingredients!" (4/272/NT). Twelve participants reported no side-effects at all.

Participant reports mostly tallied with practitioner reports, shown in the rightmost column of **Table 36**.

6.8.3.iv Incidental medical findings

One incidental medical finding was made during the study, for participant 2/174/NT at the baseline assessment. See **6.3.4** for an account of the finding and the actions taken.

6.8.4 Exploratory analysis: Findings from the process of identifying participants

Short exit interviews carried out with each PIC focused on the ways in which the search/screen process could be improved for a future trial. A small amount of qualitative data was analysed using reflexive thematic analysis, and yielded three themes: **Optimising process**; **Database codes**; **Payment provided**.

Under **Optimising process**, two PICs (PIC2, PIC3) pointed out that some exclusion criteria were database codes and therefore could have been included in the database search prior to the screening process; examples given were pregnancy (EXC8), pacemakers or other active implanted devices (EXC2), blood clotting disorders (EXC5) and chronic kidney disease (EXC3). This would have made the search/screen process more efficient and also less expensive, as it would rebalance the required time towards searching (done by an IT manager) away from individual screening (done by a clinician):

> We could have done a tighter screen on our patients, so we could have ruled out certain things alongside of what your search included… some things would have been a bit harder to search for but… there's quite a lot more we could have done at search stage (PIC2)

A virtual Site Initiation Visit (SIV) was offered, but only two PICs chose to take up the offer. The remaining two felt the notes and Help tab provided in the search/screen log spreadsheet were adequate. Asked why they had preferred to go ahead without the SIV, the PICs identified time and competing workload priorities:

> It was purely time pressure, and… the Help tab was useful, clear enough… fairly self-explanatory (PIC3)

> I think I understood how it worked… it was straightforward enough… (PIC1)

In the **Database codes** theme, all PICs felt the search process would have been easier had database codes been provided:

> Sometimes with research we get offered an EMIS search… in this case I had to make it up, which is fine for a clinician – obviously it would be more difficult for an IT technician or a manager to clinically decide which codes are the ones to use (PIC1)

> I suspect there's some places that they may prefer to have a… code list or even a search written (PIC3)

> It would have been a lot easier to have READ codes, anything like that just narrows the search criteria… (PIC2)

> I guess if it had been EMIS-specific, then it would be easier. (PIC4)

Under the **Payment provided** theme, PICs commented on whether the payment provided was adequate to cover time spent. The screening process was costed for a clinician to spend up to 10 minutes screening each patient, up to a maximum of 50 patients. In practice, clinicians tended to spend less than 10 minutes screening each patient, but often had more than 50 patients to screen:

> It depends on the record… some are well-written records with good clinical coding, which makes it obvious. Others less so. So it probably averages out (PIC3)

> You have the ones you can exclude straight away, so as soon as you open the patient's notes you're looking for obvious things like housebound, dementia, anything like that… I screened 137 and I would say that took me 4 hours (PIC2)

> I screened 40-odd and that took an overall of about two point five, I think, to three hours… I managed to do it fairly quickly (PIC1)

> It took me a full morning, maybe somewhere between four and six hours (PIC4)

6.8.4.i Findings regarding AF in primary care

Email conversations with GPs carrying out the search/screen process revealed information of interest to a future trial regarding the management of AF in primary care (Charlesworth, 2023a, 2023b), as follows:

- Although it is common (but not universal) to offer AF patients an annual check-up that includes rate and rhythm monitoring, the extent of monitoring would not detect progression of AF from paroxysmal to persistent forms. Proactive follow-up of AF patients in primary care remains limited because AF treatment in primary care is primarily aimed at risk management and stroke prophylaxis, and progression from paroxysmal to persistent/permanent AF is not in itself associated with higher stroke risk according to the recommended risk assessment tool CHA_2DS_2-VASc (National Institute for Health and Care Excellence, 2021; Lip et al., 2010). Therefore, proactive follow-up is thought to be of little value given that first-line treatment does not change. Follow-up therefore tends to be initiated by patient request instead;
- While primary care databases offer a code that differentiates paroxysmal from persistent/permanent forms of AF, according to the above it is likely that a proportion of patients coded as paroxysmal will in fact have progressed to persistent AF. The subset of Santé-AF participants wearing the CardioSTAT® monitor appeared to support this speculation.

6.8.5 Exploratory analysis: Recruitment ratios

A ratio of recruitment elements was calculated using feasibility study data to support a future trial. This was ≈ 1 PIC : 7.5 participants : 1.9 practitioners.

6.8.6 Exploratory analysis: Sampling for interview

A maximum variation sampling strategy (Benoot, Hannes and Bilsen, 2016; Palinkas et al., 2015) was used to purposefully sample n=16 interviewees on four dichotomised factors (age, sex, duration of diagnosis and previous experience of complementary therapies). This proved challenging to implement. Participants were allocated to interview solely on the four qualitative criteria across the entire subset consenting to interview (n=29 or 97.0%), and study group allocation was not a criterion; as a result, the allocations to interview did not follow the 2:2:1 allocation ratio between the study groups.

Figure 20 shows the number of interviewees against the total number in each group at baseline and follow-up.

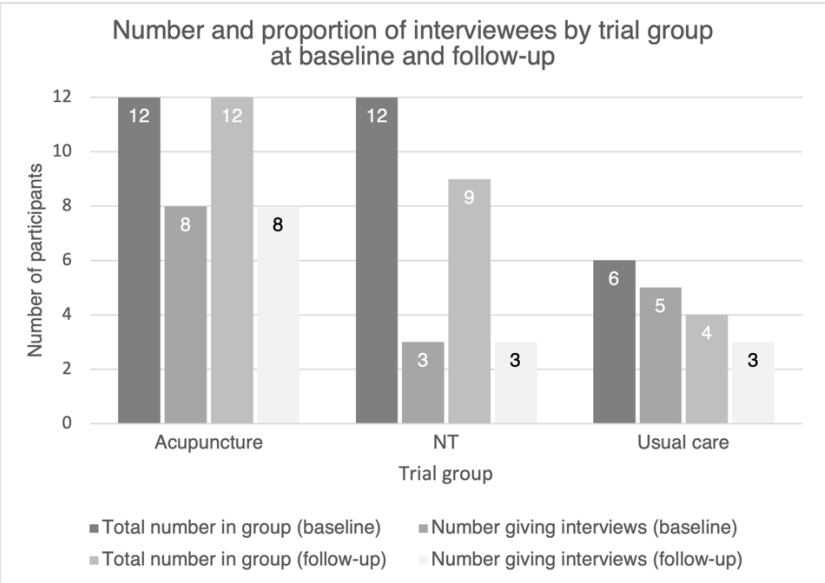

Figure 20: Number of interviewees by study group at baseline and follow-up

A second finding was that, while the maximum variation sampling strategy required 16 participants to meet all variations, the characteristics of the n=29 study population did not fulfil all variations. This meant that the sampling strategy was unsuccessful. Participants were allocated to interview where they fulfilled an unallocated variation, but seven variations were left unfulfilled and four were fulfilled by multiple participants.

6.8.7 Extracts from researcher's reflective journal

To comply with research integrity, the researcher wrote a positionality statement (Brown, 2022) (**Appendix A**, Miscellaneous section) and shared her professional identity with participants during introductory discussions. The reflective journal kept while collecting and analysing qualitative data – particularly interviews – revealed the ways in which the researcher's professional and personal positionality was activated during the study, and helped the researcher to remain mindful of the possible effects of positionality during analysis and synthesis. The extracts given here are indicative of the three main themes: **Professional "lens"**; **Boundaries**; and **Gender "lens"**. Some details have been removed to avoid indirect identification of participants.

> **Professional "lens":** Urge to make a prelim. TCM diagnosis sometimes overwhelming – need to stay vigilant because it might make me behave towards [participants] in certain ways that I shouldn't as a researcher. So hard when that TCM twitch is part of my way of seeing the world. Can't switch it off! [6th January 2022]
>
> **Boundaries:** [Participant] just gave me [a small gift] when I went to pick up the kit. I think it might have been linked to [their] tearfulness in the interview, maybe making it OK to have cried, maybe just grateful to be listened to. Normal for a patient [to give gifts to a practitioner], maybe also normal as a researcher, [I] don't know. Should prob. have said a graceful no to maintain the boundaries, but honestly just couldn't. Felt more important, humanly, to legitimate [their] emotions… But must reflect on that when it gets to follow-up – obsequiousness bias possibilities! [10th January 2022]
>
> **Gender "lens":** Shock after [participant]'s [follow-up] interview… she's shopping, cooking her own + whole household's food (+ aware she has [elderly relative] who she cooks for too which makes it extra tricky). Hadn't quite realised she's only woman in whole NT group. Where's randomisation when you need it?!… but prob. ethically good we didn't inflict that on more women… Nobody else has talked about this AT ALL. Hard to avoid the thought that… [it's] because of gender difference – rest have wives doing that for them. Note to confirm that with [practitioners]. Great material for discussion chapter [21st April 2022]

6.8.8 Practitioner safety

Private healthcare providers such as acupuncturists and nutritional therapists may decline to work with a patient for a variety of reasons including personal safety, abuse of the terms and conditions of the professional relationship, limits of professional competence, or clinical assessment requiring referral back to primary care (Complementary and Natural Healthcare Council (CNHC), 2020; British Acupuncture Council, 2015). In the acupuncturists' peer supervision group it emerged that Santé-AF's acupuncturists (who may be regarded as lone researchers in this respect (Williamson and Burns, 2014; Paterson, Gregory and Thorne, 1999)) felt their contractual obligations to the study overrode the ability to discontinue working with a patient on any of these grounds.

The training workshops emphasised the need for all practitioners to exercise their usual judgement, and to apply the normal parameters of professional conduct including the option to discontinue with any participant at any time; practitioners were reminded of this in the peer supervision groups.

6.9 Exploratory analysis: Group means and sample size calculation

For completeness, the mean scores of the primary outcome (the AFEQT questionnaire) for treatment and control groups were calculated at baseline and follow-up. No statistical test of within- or between-group differences was conducted as this was not relevant to feasibility outcomes, and the study's small sample size (including non-normality in the Usual Care group induced by the small sample size, assessed visually with a Wilcoxon signed-rank test histogram) – would have produced a misleading result. Means are shown per group in **Table 37**.

Table 37: Group means, primary outcome, at baseline and follow-up

	Acupuncture (n=12)	Nutritional Therapy (n=9)	Usual Care (n=4)
Baseline	71.1±20.4	76.2±13.9	63.4±32.3
Follow-up	81.3±13.6	85.2±12.5	76.6±20.3

Figures are mean ± standard deviation. Follow-up duration average 94 days. Higher scores = improvement.

Sample size calculations for randomised controlled trials are based on the differences between groups found at a primary endpoint either in a feasibility study or previous, congruent trials (King and Eckersley, 2019). In calculating a sample size for a future trial, the between-groups difference data generated by this feasibility study was not used due to the study's low power to detect accurate effect sizes, which may lead to inflated treatment effects and consequently underpowered future trials (Freedland, 2020; Kraemer et al., 2006). The sample size for the feasibility study was also too small to reliably balance all important characteristics between groups, including the effect modifiers identified in **Chapter 3**, resulting in some chance imbalance in these parameters at baseline (**Table 21**).

However, the feasibility study's follow-up values for n=25 participants were used to calculate a pooled standard deviation (SD) for the primary outcome (AFEQT questionnaire). Follow-up values were used in preference to within-participant change scores because of the chance imbalance at baseline, which adds variation and is more likely to detect a significant effect if the intervention is effective (Vickers and Altman, 2001).

To calculate the pooled SD, the raw AFEQT Overall scores (for 18 items on a 1-7 scale) were transformed to a 0–100 scale (St Jude Medical, 2009) for 25 participants. After transformation, higher numbers indicate better symptom-related HRQoL. Missing data (Acupuncture: n=2 (0.6%); NT: n=3 (1.3%); Usual Care: no missing data) was imputed using simple mean imputation across all other participants' scores for that question at that measurement point (Jakobsen et al., 2017). A pooled SD of 14.0 was calculated from all 25 participants' follow-up values using the STDEV formula in Microsoft Excel v16.78 (Microsoft Corp., 2023).

As demonstrated in **Chapter 3** above, there are no controlled trials of acupuncture or nutritional therapy investigating changes in AF-related HRQoL or symptoms that are of sufficient quality to guide a sample size calculation for a future trial. It is therefore not possible to identify a relevant between-groups difference at follow-up. A clinically important difference (CID) was calculated by Holmes et al. (2019) using data from 1,347 patients in the ORBIT-AF clinical registry who experienced various standard care treatments, including medication, cardioversions and ablations, over a one-year period. The authors correlated one-year change in AFEQT score with the European Heart Rhythm Association (EHRA)'s AF functional status classification scale, and found that a change of 5.4 points in the AFEQT Overall scale corresponded to a one-class improvement in the EHRA scale, making a 5.4 point change clinically important.

To detect an effect size of 5.4 AFEQT points with a standard deviation of 14.0 at 80% power with a two-sided 5% significance level, a future trial would require 106 participants per group, or 318 participants in total for a three-group trial. Adjusting for the 20% loss to follow-up indicated by the feasibility study gives a total of ≈382 participants (rounded to 385 for convenience). Adjusting again for the 2:2:1 allocation ratio gives a per-group total of 154:154:77 (Sealed Envelope Ltd, 2012; Julious, 2004).

This sample size should be interpreted with caution, because Holmes et al.'s CID was calculated within participants; the assumption that the between-group difference at follow-up will be the same as the within-group CID over time may not be valid. Holmes et al. explicitly excluded from their analysis any patient who did not experience a change in either AFEQT or the EHRA scale during the one-year period, noting that "the interpretation of the CID is within the patient in the sense that it reflects differences that would be expected for a patient who has an important improvement" (p.3). In a future trial – in which improvement is not likely to be universal and effect sizes may therefore be smaller than Holmes et al.'s 5.4 points – there is a possibility that a sample size calculation based on this "effect size" would underpower the trial. However, this may be offset by the larger treatment effects that could reasonably be anticipated in a superiority trial in which adjunctive therapies are added to the standard care treatments tracked by Holmes et al. These factors should be borne in mind when interpreting this sample size calculation.

6.10 Overall feasibility

Feasibility is evaluated per objective, above, using pre-determined progression criteria. **Table 38** brings together the determinations for all objectives, resulting in a summary judgement based on the quantitative evidence and using a traffic-light system to indicate feasibility visually (Bond et al., 2023; Chan et al., 2021; Avery et al., 2017; Eldridge et al., 2016a).

Table 38: Feasibility of Santé-AF by objective

Objective number	Description	Measurement	Feasibility threshold	Level achieved	Feasibility of domain
1	Participants' willingness to take part	Percentage of eligible participants randomised	≥90%	96.8%	Yes (green)
2	Appropriateness of eligibility criteria	Percentage of identified participants eligible	≥60%	14.1%	No (red)
3	Participant retention	Percentage of randomised participants retained	≥80%	83.3%	Yes (green)
4	Acceptability of interventions	Participant report of allocation satisfaction @ 7–10 on 10-point scale*	≥75%	75.0%	Yes (green)
		Participant report of intervention acceptability @ 1–3 on 7-point scale**	≥75%	95.0%	Yes (green)
5	Acceptability of assessments	Completeness of main outcomes data	≥80%	90.0%	Yes (green)
		Participant report of assessment acceptability @ 1–3 on 7-point scale**	≥90%	88.0%	No (amber)
6	Utility of CardioSTAT® monitor	Participant report of monitor influence on participation @ 1–2 on 5-point scale***	≥50%	11.1%	(abandoned as inappropriate)
		Correlation between AF episodes recorded by ECG monitor and symptom diary	≥1 episode	–	(abandoned as analysis not viable)
7	Participant experience of study participation	Participant report of participation acceptability @ 1–3 on 7-point scale**	≥75%	96.0%	Yes (green)

* higher numbers = greater satisfaction ** lower numbers = greater acceptability *** lower numbers = greater influence

Following the guidance offered by Mellor et al. (2023), the progression criteria were interpreted as guidelines rather than absolute rules, and a judgement of feasibility was taken on the whole set. As the table shows, two domains were abandoned as inappropriate or unviable, leaving eight domains. Six of these met or bettered their progression criteria, while a seventh (participants' report of assessment acceptability) was considered to have been met.

Cumulatively, the progression criteria demonstrate the overall feasibility of a future trial based on the current design. However, a determination of feasibility according to quantitative progression criteria tells only part of the story, particularly in the context of a pragmatic trial (Aschbrenner et al., 2022; Chan et al., 2021). In **Chapter 7**, these results will be critically discussed and recommendations made for changes to a future trial's design to enhance feasibility.

7 Discussion and recommendations

In this chapter, the outcomes of feasibility assessment are critically discussed, bringing together quantitative and qualitative data to reach a more nuanced understanding of the study's design in relation to the population and interventions investigated. For ease of reading, the chapter is structured, like the Results, around the feasibility objectives; however, overall feasibility is considered to be an interdependently constructed attribute (Mellor et al., 2023), and in cases where a recommended change affects additional trial variables or parameters, multiple objectives are discussed together. The discussion results in a number of recommendations to increase a future trial's operational feasibility, and a number of additional suggestions that are not required to reduce uncertainty but may be considered to increase the reliability and real-world generalisability of a future trial's results.

7.1 Objective 1: Willingness to take part

7.1.1 Feasibility of objective 1

The progression criterion for objective 1 measured the percentage of eligible participants randomised, with a threshold of ≥90%; Santé-AF achieved a randomisation level of 96.8% of the total eligible participants, thereby meeting its progression threshold. This compares favourably with similar feasibility studies in acupuncture or nutrition including Feingold et al. (2023) (57% of eligible patients enrolled); Hargreaves, Harding and Clarkson (2021) (49.2%); Jia et al. (2020a) (82.0%); and Cramon et al. (2021) (19%). The "most important reasons" (

Table 22) accord with current research: wanting to help others and personal benefit including wanting to avoid taking medication (Lee et al., 2017).

Table 23 shows that five (of n=16 offering explicit reasons for declining to participate) declined for reasons relating to the COVID-19 pandemic. This impediment would automatically resolve unless a future trial took place under similar conditions.

Santé-AF's randomisation level, expressed as a percentage of the eligible total, may be artificially high because the study used an extensive set of eligibility criteria that required two stages of screening; by the second screening stage a degree of attrition had occurred, meaning that the numbers willing to take part were closer to the numbers eligible, giving a high proportion of randomised to eligible participants.

This objective was feasible in that sufficient participants were willing to participate, and to be randomised; no changes to the trial design were found necessary to increase feasibility. However, two important issues are discussed below in relation to participants' willingness to take part: first, the effect of preferences; second, the effect of eligibility criteria.

7.1.2 Effect of preferences

The exploratory analysis of data collected during the pre-consent queries phone call (**6.1.3**) suggests that preferences or aversions may have contributed to unwillingness to be randomised for 28 (50.0%) of n=56 patients who received the queries phone call (Wasmann et al., 2019; Corbett, Watson and Eastwood, 2016). Despite this, only three participants explicitly declined to take part due to an aversion to one of the study interventions (**Table 23**); the true number of patients self-excluding on the basis of a preference or aversion cannot be known.

In an unblinded trial, participant preferences have potentially greater influence than in a blinded trial (Torgerson, Klaber-Moffett and Russell, 1996), and it has been demonstrated that preference effects may have greater impact than treatment effects, particularly when using subjective outcome measures (Walter and Bian, 2020; McCaffery et al., 2011; Janevic et al., 2003). However, these findings are not universal; a recent meta-analysis of 44 partially randomised patient "preference" trials found that preference did not influence the primary outcome (within a preference trial) (Wasmann et al., 2019). Likewise, in a Korean trial of acupuncture for AF, no patient questioned their assigned treatment group (Lee et al., 2017). These findings were at variance with those of Santé-AF, in which preferences persisted after randomisation: the most frequently and strongly expressed preference was for acupuncture (**6.4.1.ii**).

Santé-AF's participants were willing to participate and to be randomised; however, for reasons of generalisability and to preserve integrity of trial parameters, it may be advisable to take account of

preferences in a future trial's design and analysis. In Santé-AF, post-consent preferences – what Power and Hopayian (2011) call "cognitive measurement biases" – may have exerted a range of effects including positive response to treatment in a preferred group (a placebo effect) (Preference Collaborative Review Group, 2008) or resentful demoralisation leading to poor adherence, degraded patient-practitioner relationship, poor response to treatment (a nocebo or "frustrebo" effect) or loss to follow-up when allocated to a non-preferred group (Alibhai et al., 2022; Wasmann et al., 2019; Power and Hopayian, 2011; Kwan, Dimidjian and Rizvi, 2010). One example of this in Santé-AF may have been the report of nutritional therapy (NT) practitioners that the initial patient-practitioner relationship was not as strong as it would be in a real-world context (**6.7.3**), an effect which may have been related to the status of NT as the most frequently non-preferred intervention. Additionally, one participant withdrew as a result of being randomised to Usual Care in the context of a preference for a treatment group (**6.3.4**).

For participants in the NT group, the effect of any aversion to NT or preference for acupuncture may have been compounded by the effort involved in adherence to the NT intervention, resulting in poor adherence or attrition. It is certainly the case that the NT group saw higher attrition than the Acupuncture group (**Figure 7**), although it is not known whether this was (even partly) an effect of preference combined with the effort of adherence. Substantial withdrawal due to preference may present issues for a future trial in terms of differential loss to follow-up (Wasmann et al., 2019; von Essen, 2015), potentially compromising power to detect true effects of the interventions.

Another argument for taking account of preference concerns the possible generalisability of a future trial's findings to wider real-world contexts (Zuidgeest et al., 2017a; Burchett, Umoquit and Dobrow, 2011) especially when considering the real-world context of privately provided healthcare interventions. In real-world contexts in the UK, acupuncture is provided within the state healthcare delivery system for certain conditions (e.g. chronic pain and cancer care (National Institute for Health and Care Excellence (NICE), 2021; Seers et al., 2009)), but not for AF; NT is not provided within the state healthcare delivery system for any condition (National Health Service, 2022a). Therefore for AF patients, both therapies are only available as private healthcare, paid for by the patient at the point of delivery. The means that, in a real-world context, these interventions are conditioned by a high degree of individual patient preference and choice, including choice of therapy itself and choice of practitioner. Choices are guided by a wide range of factors including interest in the therapy, beliefs or evidence about its effectiveness for the condition, personal recommendations, practitioner clinical specialisms, qualifications and affiliations, and practical considerations such as clinic location, hours and parking availability (Tangkiatkumjai, Boardman and Walker, 2020; Bishop and Lewith, 2008; Bishop, Yardley and Lewith, 2006). This degree of choice may be considered to have a material impact on a number of treatment aspects, including

engagement, adherence, and outcome (Alibhai et al., 2022; Le et al., 2018); where choice is not exercised, many aspects of treatment may be affected. The observation of one Santé-AF practitioner is worth reiterating here:

> Normally the therapeutic relationship starts before you even see them… they've done some searching, they've found you, they've chosen you… and by the time you actually see them, that investment, that commitment, it's already started. When a client has not paid for [this therapy], when a client has not chosen [this therapy], then you don't get them as invested in it (P4/NT)

This observation is supported by some evidence indicating that simply giving patients a choice of intervention, rather than randomising them, may in itself exert some effect, i.e., selection effects (Walter et al., 2012); as Wasmann et al. observe, "perhaps consciously choosing a treatment ensures a certain dedication and tolerance for the treatment" (2019, p.9). For instance, a trial of two therapies for PTSD found that allowing participants to choose their treatment gave better quality-of-life outcomes than either randomised allocation or allocation to a non-preferred treatment, suggesting that the exercise of choice was itself a non-specific effect of treatment (Le et al., 2018). In addition, enabling choice may improve participant retention (Carlisle et al., 2022; Brueton et al., 2013).

Of the two interventions studied in Santé-AF, NT in particular warrants consideration of participant choice alongside related questions of burden and adherence. Participants perceived the NT intervention as requiring substantial effort and cost to maintain adherence (**6.4.2.iii**). To some extent this is unavoidable, as the nature of the therapy – particularly in the restricted scope practised in this feasibility study – is to promote health through dietary change; therapeutic responsibility is devolved to the patient and effected through adherence to recommendations (see also the discussion regarding adherence in **7.4.3**). Seen in this light, there may be a substantive difference between choosing NT in the real world and having it "foisted upon [you]" (P5/NT) via randomisation in a trial, with potential effects on adherence in particular. The only NT participant who took primary responsibility for their own diet, and therefore experienced the full burden of change, contributed some perceptive reflections on the score of personal motivation that are relevant here:

> [NT] makes you think about yourself… it makes you do it yourself, in a way. And that's… a big commitment curve… You've got to want to do it long-term, really. And I think *that's a decision you have to make yourself* (4/272/NT) [my emphasis]

In designing a future trial, it is assumed that these interventions would continue to be provided privately; therefore a pragmatic trial of these interventions should ideally attempt to reflect as many real-world attributes of the interventions as possible within the conventions of pragmatic trials methodology. But there are conflicts between trials methodology and the real world: for instance,

even the most pragmatic trial would not expect participants to pay for their own treatments because although this is an important influential factor in real-world contexts, in a trial this would place burden on participants, discouraging them from taking part and introducing biases (such as socioeconomic differences) that may influence treatment effects and compromise generalisability of the results (Williams et al., 2023; Naidoo et al., 2020; Bishop and Lewith, 2008; Conboy et al., 2007). A research question investigating such intensively real-world parameters as these may be best conducted as an observational design, such as audit or natural experiment (although this would not overcome selection biases either). It must therefore be concluded that – to the extent that these real-world parameters may substantially impact outcomes – the results of a future trial using the current design would have only limited generalisability to a real-world context in which interventions continued to be provided privately. This must be regarded as an insuperable limitation.

7.1.2.i Preference designs for a future trial

There may be grounds for a future trial to consider a preference design that would take account of both selection effects (the effects associated with the exercise of choice) and preference effects (the effects associated with receiving, or not receiving, a preferred treatment) (Walter et al., 2012; Bower et al., 2005; King et al., 2005).

Various preference trial designs have been put forward, including the patient preference/comprehensive cohort design (Brewin and Bradley, 1989); Zelen's single or double methods of pre-randomised consent (Zelen, 1979); the preference-informed complementary trial (PICT) (Ali et al., 2021); the two-stage randomised design (Rücker, 1989); and the approach of simply accounting for preference in the analysis of an ordinary RCT (Torgerson, Klaber-Moffett and Russell, 1996). All of these designs have some shortcomings in relation to a future trial of Santé-AF.

The Brewin-Bradley patient preference design randomises only those patients without a preference and purposefully allocates others to the preferred intervention; this attenuates the effect of preference to some extent (Preference Collaborative Review Group, 2008). The approach is pragmatic, answering questions of "which treatment is more useful under what are judged to be optimal conditions of motivation?" (p.315); but the design may introduce bias due to limited randomisation which cannot sufficiently balance the influence of known and unknown between-group characteristics (Ali et al., 2021).

Zelen's method randomises patients prior to seeking consent, with only those in the intervention arm(s) being approached for consent; those refusing consent are allocated to usual care, while in a "double consent" variation, those refusing consent may be offered the intervention itself. Both single and double consent methods accommodate patient preference and avoid resentful demoralisation in a usual care group, as these participants are unaware of being in a trial. However, participant

crossover may render statistical analysis of effectiveness less robust (von Essen, 2015); additionally, the non-routine nature of Santé-AF's assessments makes Zelen's methods untenable, since the usual care group would be required to attend assessments, breaching ignorance of trial participation and potentially introducing the biases that the methods otherwise avoid (Torgerson and Roland, 1998).

Ali et al.'s preference-informed complementary trial (PICT) approach deals with an aspect of unwillingness to be randomised in the context of aversion to a specific intervention (Ali et al., 2021). The PICT design runs two "sister" trials side by side, one offering all possible interventions, and the other offering all interventions except the one subject to aversion; patients choose their "preferred" trial based on aversion or absence of aversion, and are randomised as usual within the chosen trial. This design was conceived as a way of investigating three pain medications in a paediatric musculoskeletal injury context, where opioids were one of the medications being trialled; there was an aversion to opioids on the part of parents giving consent for children randomised into the trials and also, due to the context, the trials did not incorporate a "no treatment" control. The benefit of the PICT design is the strong element of randomisation while catering for unwillingness to be randomised due to aversion; the disadvantage, as with all exercise of preference, is that populations in the two trials may differ in other respects in addition to, or related to, their aversion. The authors point out that if the effects of preferences do not influence the treatment effect (presumably if a first analysis of treatment effect between the groups in the sister trials correctly accepts the null hypothesis) then the population of the two trials may be pooled and analysed together, providing greater power; but the sample size required to reliably detect differences between the two trials' respective treatment groups is likely to be large. In mitigation of this, the authors propose a pooled treatment effect estimation only if baseline characteristics between the two trials do not reach a "maximum tolerated difference" determined by feasibility/pilot data and clinical rationale regarding whether specific patient characteristics may be effect modifiers – a decision-making process that may be prone to some bias.

The extent to which a PICT design may be appropriate to a future trial of acupuncture and NT is moot. First, the design caters for aversion; it is not known how many patients self-excluded from Santé-AF on the basis of aversion, but the small amount of evidence from pre-consent stage suggests that *aversions to* were less prevalent than *preferences for* the interventions both before and after randomisation (**6.1.3**, **6.4.1.ii**). Second, the PICT design would be expensive to implement and may not recruit sufficient numbers to fulfil a large sample, because allowing for two aversions would call for three sister trials (and even three sister trials do not allow for an aversion to usual care, as observed in Santé-AF).

In a two-stage randomised preference design (Rücker, 1989), patients undergo a first randomisation to either a "randomisation" or a "choice" group to mitigate baseline imbalances across the cohort. Following this, the choice group is offered a choice of intervention while the randomisation group is randomised as per a standard RCT; in an adaptation of this design, participants in the choice group without a preference are randomised (effectively a crossover from the choice group to the randomisation group). This design would allow the effect of preferences to be robustly analysed, in particular mitigating the effects of selection bias within the choice group, but does not avoid the possible depressive effect on recruitment observed in Santé-AF, arising from participant preferences pre-randomisation (Walter et al., 2017) – although, if recommendations are adopted to widen eligibility criteria, below, this effect may not impact strongly on a future trial's recruitment.

The "ordinary RCT with preference as a covariate" approach asks participants about any preferences prior to randomisation and adopts these as covariates in analyses of effect (Torgerson, Klaber-Moffett and Russell, 1996). This retains all the internal validity associated with maintaining full randomisation in a manner that can be explained to participants simply. A further substantial advantage of this approach over a preference design is its predictability in terms of group numbers, therefore giving some certainty to triallists regarding recruitment of practitioners, and to practitioners themselves regarding numbers of participants. Balanced against this, the approach does not reflect real-world conditions by offering a choice of therapy, and it cannot address unwillingness to be randomised in the case of strong preference or aversion.

It can be seen that all preference designs, except the "ordinary RCT with preference as a covariate", are subject to a degree of confounding relating to choice in that participants who choose their intervention may differ in one or more characteristics (that may impact on outcomes) from participants who choose another; the effect of choice is potentially to negate the effect of randomisation in this respect. Additionally, all designs call for an increase in sample size to maintain power adequate to demonstrate the effects of both intervention and preference (Walter et al., 2012). Practically speaking, an additional effect of a preference design would be to create volatility in a future trial's parameters, including ratios of participants to practitioners, which may lead to consequent volatility in other dimensions including practitioner recruitment (practitioners may be less willing to participate if their numbers of allocated patients, or duration of trial commitment, are uncertain).

It remains questionable whether this feasibility study found sufficient evidence of preferences affecting adherence, or whether the replication of real-world choice is sufficiently imperative, as to warrant being a focus of investigative attention. Such a radical shift in design would render many of the current feasibility study's findings irrelevant, and would therefore be likely to require its own

feasibility study before proceeding to a large-scale trial; even after a further feasibility study, the parameter volatility noted above is unlikely to become stable, although it may be better understood. While preferences and aversions in the feasibility study were marked, it remains the case that feasibility of the key parameters addressed by preference designs (recruitment, allocation satisfaction, adherence and acceptability of the interventions) was high (**6.1.11**, **6.4.1**, **6.4.2.ii**, **6.4.5.ii**). This suggests that preferences, while marked, did not exert a sufficiently strong influence as to necessitate the adoption of a preference design.

Recommendation: A future trial should not adopt a preference design, but instead should maintain its current design and take account of preferences for treatment, together with treatment expectation, as covariate in analyses.

7.1.2.ii Choice of practitioner

Separately from considerations of preference for therapy, the choice of practitioner is a key factor in the real-world experience of both acupuncture and NT. As argued above, choice in any dimension may affect other variables such as treatment effects, adherence and attrition, and potentially put a future trial at risk of selection biases.

In Santé-AF, participants were not offered a choice of practitioner, but instead were matched to practitioners by the researcher purely on the basis of appointment availability. Offering a choice of practitioner in a future trial may mitigate non-adherence, including non-adherence resulting from location (e.g., the case of 3/684/A (**6.3.4**)); this is particularly important if NT practitioners are required to hold consultations in person in a future trial.

Balancing this, offering a choice of practitioner is likely to generate some volatility in a future trial's parameters. For participants, the chosen practitioner's availability may lengthen timescales and delay the start of treatment, potentially increasing attrition; for practitioners, commitment to the trial would be less clearly defined over a longer duration and may therefore depress recruitment. Perhaps the strongest contraindication is the fact that, as argued above, the exercise of choice (in any dimension) appears to be associated with a range of effects that may, in this case, inflate the outcomes of both acupuncture and NT groups in comparison to usual care. Unless a future trial were to adopt the two-stage randomised preference trial described above, which would mitigate this bias, practitioner choice cannot be accommodated without introducing some bias.

Recommendation: It is recommended that a future trial should continue to allocate participants to practitioners on the basis of appointment availability; but also that a range of practitioners local to PICs' catchment areas should be recruited to the trial, and that participants should be matched with practitioners on the basis of both appointment availability and location.

7.1.3 PICs' and practitioners' willingness to participate

This objective also considered the willingness of practitioners and Participant Identification Centres (PICs) to participate. No progression criteria were set, although important elements of feasibility were associated with both. It is suggested that future feasibility studies recruiting from primary care and delivering interventions via the private sector should set progression criteria for the recruitment of both PICs and practitioners.

At feasibility study stage, sufficient practitioners and PICs were willing to take part to achieve the target sample size; quantitatively speaking, no changes to a future trial's design are required. Willingness to participate may be enhanced on the basis of various feasibility study findings that identified important elements making the trial attractive to both practitioners and PICs (**6.1.6**, **6.1.8**).

Recommendation: Elements enhancing attractiveness should be emphasised in practitioner/PIC recruitment material for a future trial, to maximise willingness to participate.

7.1.3.i Bias in practitioner recruitment

The recruitment of Santé-AF's practitioners may have been affected by three specific characteristics of the feasibility study, arguably all types of centripetal bias:

1. **Location of the study:** The area in which Santé-AF was conducted (York, UK) has a higher-than-average number of acupuncturists and nutritional therapists (NTs) due to the location of the study centre where many practitioners of each therapy train (Northern College of Acupuncture, 2023). This provides a larger pool of potentially eligible practitioners than would be typical in most other areas of the UK (British Acupuncture Council, 2023; British Association for Nutrition and Lifestyle Medicine, 2023).
2. **Professional relationships:** Santé-AF practitioners were attracted to the study via existing professional relationships with the researcher (**6.1.6**). Selecting "'enthusiastic' centres" (Avery et al., 2017, p.6) may lead to overestimation of parameters – in this case, practitioner recruitment rates – for a future trial (Ukoumunne et al., 2015; Lee et al., 2014).
3. **Researcher's professional qualification:** Santé-AF's acupuncturists in particular were attracted by the fact that the researcher was an acupuncturist, feeling that this lent validation to a methodology (i.e., the RCT) that has a reputation in the profession as being antithetical to traditional Chinese medicine (TCM) (Brosnan, 2016; MacPherson and Thomas, 2008). A future trial that did not have a TCM acupuncturist in a design, and/or practitioner-facing role may have more difficulty in recruiting TCM acupuncture practitioners.

In view of these biases, achieving overall practitioner recruitment rates (and the resultant accommodation of participant sample size) may be more difficult for a future trial than in the feasibility study. Several strategies could be adopted to mitigate the risk of practitioner under-recruitment.

Recommendations: A future trial should adopt more cautious target ratios of eligible to recruited practitioners than the ≈4:1 (acupuncturists) and ≈2:1 (NTs) found in the feasibility study. It may be advisable to open future trial sites/local areas by first recruiting practitioners (or at least seeking agreements in principle) and recruiting the "upstream" elements of the ratio of PICs : participants : practitioners accordingly (**6.8.5**). Practitioner eligibility criteria may be reconsidered to potentially identify greater numbers of eligible practitioners, balancing this with safety requirements (see **7.2.2 below** for a discussion of this). Finally, a future trial could plan for a longer duration of practitioner recruitment than Santé-AF's three weeks. All strategies could be adopted concurrently.

7.2 Objective 2: Appropriateness of eligibility criteria

7.2.1 Feasibility of objective 2

The progression criterion for objective 2 measured the percentage of patients identified by the PICs that were eligible, with a threshold of ≥60%. Santé-AF found that just 14.1% of the total identified were eligible, thereby not meeting the progression threshold (**Table 24**). This figure should be interpreted cautiously, as the final stages of eligibility checking were not carried out until a late stage of recruitment, by which time a degree of natural attrition had occurred. **Table 24** shows that the largest proportion of participants was not excluded by eligibility criteria, but in fact were not willing to participate (i.e., did not return permission-to-approach forms).

However, the feasibility study's eligibility criteria introduced selection bias, as they isolated a narrower subset of the AF population than is representative of the real-world equivalent (Rengerink et al., 2017). Had more pragmatic eligibility criteria been used, not only would selection bias have been mitigated, but a larger number of potential participants would have been identified and a proportionately larger number may therefore have been eligible to participate. This would also help mitigate any regression to the mean effects remaining after randomisation (Anheyer et al., 2023; Hengartner, 2020; Morton and Torgerson, 2005) although the degree of between-participants heterogeneity conferred by wider eligibility criteria may require an increased sample size.

Widening the eligibility criteria of a future trial would therefore have several advantages – not only increasing confidence in the trial's generalisability to a wider AF population, but also reducing

burden for participants, reducing potential randomisations in error, and simplifying several operational parameters including identification of participants and eligibility screening.

Criteria that may be reconsidered include those that were added due to the COVID-19 pandemic (INC6, 7; EXC11); the effect of these in Santé-AF appeared relatively small, although it is not known how many patients self-excluded on this basis without communicating this. These criteria could be removed for a future trial (assuming that it did not take place under similar pandemic conditions). Assuming a future trial maintained the traditional approach to consent (see **7.8.2.ii below** for a discussion of this), other criteria may also be thought unnecessary as they are explicitly set out in consent materials (INC8, 9, 10).

7.2.1.i Other eligibility criteria to be reconsidered

INC1: Aged ≥45≤70: Excluding participants outside this age range removed over 74% of participants from the feasibility study (**Table 25**). Removal of the upper limit is particularly indicated by the nature of AF, which increases in prevalence with age (Adderley et al., 2019): UK prevalence estimates increase from an average 4.7% in the age bracket of ≥45≤69, to an average 26.4% in the age bracket ≥70≤84 (Public Health England, 2017) (although the caveats on these estimates should be noted (**2.1.3 above**)). It is recommended that a future trial should consider increasing the upper age limit, while balancing this with intervention- and assessment-related burden for a population of older adults. For the same reasons, the lower age limit could be removed; while AF prevalence below the age of 45 is estimated at just 1.5% (Public Health England, 2017), removal of the lower age limit would also increase confidence in the real-world generalisability of the trial's findings.

INC2: Limits on diagnosis period: While a "settling in" period after diagnosis may still be needed to exclude transient AF, the distal limit (≤60 months prior to screen date) could be removed. This would act in tandem with a relaxation of age limits to reflect a real-world AF population more closely.

However, the complexity of AF as a health condition suggests that the criteria of age and diagnosis period are important prognostic variables (Roberts and Torgerson, 1999). Debating the puzzling heterogeneity of results from trials investigating the effects of Omega-3 polyunsaturated fatty acids (PUFAs) for the prevention of cardiac arrhythmias, Ramadeen and Dorian (2011) propose that this particular therapeutic may be more effective for patients whose AF is more long-standing and has already provoked structural remodelling/myopathy in the atrial substrate, typically manifesting as the emergence of one or more comorbidities sharing the same pathogenetic mechanisms. If this selective effect is true for PUFAs, it may also be true of other therapeutic approaches. While pragmatism requires wide eligibility criteria, it may be important either to include duration of diagnosis/number of comorbidities as covariate in analyses, or perhaps (given sufficient power) to

stratify for these variables during randomisation. Note that the two participants randomised in error on grounds of AF onset outside the 60 month period specified by the feasibility study's eligibility criteria (**6.2.1**) would not, under these conditions, be excluded.

INC4: Self-detectable paroxysmal AF of at least weekly frequency: In the feasibility study, participants needed to be aware of symptoms to complete the diary, hence the "self-detectable" stipulation. However, up to 40% of the AF population is asymptomatic (Ballatore et al., 2019), and those who are symptomatic may feel symptoms less frequently than weekly; as a result, the perceptibility aspect functioned as a significant limitation of the study by potentially excluding a large proportion of potential participants. Perceptibility of symptoms, and its impact on a future trial, is further discussed in **7.6.2.i below**.

The stipulation of *paroxysmal* AF – specified in a "rather explanatory" spirit of selecting participants for whom the intervention was thought to offer most benefit – should also be reconsidered by a future trial. According to baseline CardioSTAT® data, AF appeared to be constant throughout the duration of analysable data for 50.0% of participants (5 of n=10) (**Table 33**), suggesting that these participants' AF had progressed from paroxysmal to persistent. PIC databases do distinguish between paroxysmal and other forms of AF, but while AF is often followed up annually in primary care (Bakhai et al., 2013), the monitoring carried out during follow-up may not be sufficient to detect progression from paroxysmal to persistent AF (**6.8.4.i**). A proportion of patients coded as paroxysmal may therefore in fact be experiencing persistent AF, with progression having gone undetected. This suggests it would be infeasible for a future trial to enrol only patients with paroxysmal AF unless patients were monitored for seven days or longer at baseline (which would add to costs and timescales, potentially decrease recruitment, and decrease generalisability of a future trial's findings to a general AF population). However, as the progression of AF indicates a disease state of some severity and/or duration with concomitant remodelling of the atrial substrate, this eligibility criterion may also affect the understanding of the investigated therapies' effects, similarly to the criteria of age and diagnosis period discussed above; this was corroborated by Li et al.'s review of acupuncture trials for AF, which found that acupuncture was more effective for paroxysmal than for persistent AF (conversion to sinus rhythm RR=1.1, 95%CI=1.0–1.2) (Li et al., 2022b). Controlling for this variable as observed at baseline, may be important in analyses; however, accurate determination of this variable at baseline would call for use of the CardioSTAT® monitor, which would increase costs. It may be considered a workable strategy to use duration of AF diagnosis, as discussed above, as a proxy for type of AF, and control for this variable during analysis; the restriction of eligibility criterion to paroxysmal AF only could then be removed. Note that the participant randomised in error due to having undisclosed permanent rather than

paroxysmal AF (**6.2.1**) would not, under these conditions, be excluded. This would increase the real-world generalisability of a future trial's results.

INC5: Owner of, and able to use, a mobile phone: This criterion was included to facilitate study communications, but may be inappropriate as an eligibility criterion. While INC5 did not appear to exclude any Santé-AF participant, it is not known how many patients self-excluded on this basis. It would be possible for trial personnel to communicate by letter and phone call to a landline in addition to, or instead of, mobile phones and email where participants preferred these. This may be helpful for recruitment if the upper age limit was revised in a future trial. However, the methods of collecting data on allocation satisfaction and treatment expectation would need revision for all participants; if other recommendations for the timing of randomisation are adopted, this data could be collected via the baseline questionnaire.

INC11: Speak/understand English well enough to engage with interventions and assessments: The study had no budget to fund translators. It is not known how many participants may have self-excluded on this basis. The recruited cohort in Santé-AF all spoke English as their main language; this is representative of the study's local demographic, where English is the main language for 94.9% of the population (Office for National Statistics, 2022). A future trial may establish other sites/local areas where a higher proportion of the population may not speak English as their main language. In such a case, it is recommended that participants who require translation support during interventions should be encouraged to ask a friend or family member to accompany them to appointments, which reflects routine practice. Equally, friends or family members may accompany participants to assessments. This criterion could then be removed.

EXC1: Valvular AF: At the time of Santé-AF's design this criterion was supported by the literature, which suggested that AF relating to valvular disorders was not amenable to treatment (Fauchier et al., 2015). This distinction has since been elided in the literature, justifying removal of this criterion (Hindricks et al., 2020). If symptoms and HRQoL may be thought of as somewhat independent measures, there may be additional rationale to include valvular AF patients in a future trial; HRQoL may be responsive to acupuncture or NT even if AF symptoms are not.

EXC4: Diagnosed with terminal or severe illness: This exclusion criterion was added to reduce participant burden and loss to follow-up for severely ill patients. It is recognised that this was positioned as a binary characteristic and therefore excludes participants who may be willing and able to take part despite their diagnosis. During Santé-AF, this exclusion was challenged by one participant and the relevant PIC as being inappropriate; it is also potentially unethical (Biros, 2018). It is recommended that in a future trial, this criterion should be a matter of clinical judgement by the PIC, potentially covered by the existing EXC13.

EXC6: Diagnosed with any condition contraindicating moderate exercise: This criterion was included for safety reasons, but during the study practitioners commented that it was within usual scope of practice to explore with the patient whether suitable, adapted forms of exercise would be safe and acceptable. It is recommended that this criterion should be removed, and the recommendation of appropriate exercise left to practitioners' clinical judgement.

EXC10: Current or recent acupuncture/NT: This criterion was added to prevent an avoidable confounding factor, but is less than pragmatic. It is recommended that this should be removed. Data on recent acupuncture/NT should be collected, and controlled for in analyses.

Recommendation: A future trial should re-examine the above eligibility criteria and adopt the recommendations above to maximise the generalisability of a future trial's results to a real-world AF population. It should also consider the advisability of stratifying or controlling for a range of variables: most importantly, duration of diagnosis, age, comorbidity burden and duration of comorbidity, recent acupuncture/NT, and/or baseline extent of AF.

Recommendation: If the recommendation to implement wider eligibility criteria is adopted, a future trial should recalculate the ratio of PICs : participants : practitioners (**6.8.5**) to adjust for the effect of widened criteria, using figures given in **6.2.1** as a guide. This will produce a different ratio of participants to PICs, which can be used to aid recruitment.

7.2.1.ii Violations of eligibility criteria and randomisations in error

There were four violations of the eligibility criteria during the feasibility study. The case of the participant randomised despite having a terminal diagnosis is discussed above. Additionally, three participants were randomised in error, having not revealed characteristics that would have rendered them ineligible. Two participants disclosing an ineligible AF onset date should have been excluded at identification stage; their inclusion may have been a record-keeping error or a poor application of search process by the PIC, or conversely a memory error on participants' parts. The third participant disclosed a diagnosis of permanent AF, which is not a clinical diagnosis but a decision by patient and clinician to attempt no further treatment; again, this participant should have been excluded by the PIC but records may not have been up-to-date. All four participants were retained in analyses on the grounds that feasibility was unlikely to have been affected by any of these violations.

Simpler and more inclusive (therefore more pragmatic) eligibility criteria, as described in this section, would have rendered all four participants eligible for the study, and would also allow for out-of-date or erroneous codes in patient records; it would also help to mitigate the possibility of selection bias in a future trial.

7.2.1.iii Effect modifiers and baseline characteristics

Chapter 3 identified a range of important modifiers of treatment effect, including the length of AF diagnosis, and the number, type, duration and severity of comorbidities. The feasibility study did not collect data on the severity or duration of comorbidities, but did demonstrate the feasibility of collecting data on duration of diagnosis, the number and type of comorbidities, the characteristics of standard care and changes to standard care during intervention periods, together with data on setting, dose and mode of administration of the interventions. However, some of this data was collected by participant self-report and may have been imprecise; a future trial may wish to collect this data from patient records.

Participant characteristics (**Table 21**) were somewhat unbalanced between groups, due to small sample size overall and unequal allocation ratio. There were several important imbalances that may affect outcomes if replicated in a future large-scale trial:

- the mean number of comorbidities per participant (higher in the Usual Care group than in the intervention groups);
- the mean score on the primary outcome (AFEQT questionnaire) is imbalanced (between all three groups, and notably lower in the Usual Care group than in the intervention groups);
- the mean duration of AF diagnosis is shorter in the Usual Care group than in the intervention groups.

Although it is anticipated that a future trial with an appropriate sample size would mitigate this imbalance, any chance imbalance in these characteristics in particular should be corrected during analysis, since all are important modifiers of effect as identified in **Chapter 3**, and therefore have the potential to affect outcomes.

Recommendation: A future trial should collect complete data on the effect modifiers identified in this study's systematic review, including length of AF diagnosis; number, type, duration and severity of comorbidities; changes to standard care during intervention periods; and data on setting, dose and mode of administration for interventions. This study demonstrated the feasibility of collecting data on these characteristics. However, the duration of AF diagnosis was self-reported by participants and may be imprecise as a result; it is recommended that a future trial should collect this information from PICs direct, along with duration of comorbidity diagnosis (not collected by this feasibility study).

7.2.2 Practitioner eligibility and characteristics

Practitioners were recruited according to a list of criteria intended to uphold safety and professional standards, but may have produced an unrepresentative sample of practitioners from each therapy.

The requirement for all practitioners to be qualified at minimum Bachelor's degree level in their therapy excluded two nutritional therapists, both of whom had achieved professional diplomas. Nutritional therapy is a relatively new discipline, and qualification levels have not yet been standardised (Complementary and Natural Healthcare Council (CNHC), 2022); it could be argued that the minimum qualification level rendered the NT practitioners on the study an unrepresentative sample of the profession. Balancing this, safety studies in acupuncture (there are none in NT) conclude that safety increases as education and training standards increase (Chan et al., 2017; Witt et al., 2009).

The requirement for all practitioners to be members of either the British Acupuncture Council (BAcC) or the British Association for Nutrition and Lifestyle Medicine (BANT) may also have produced a sample of practitioners unrepresentative of their professions. While these are the leading membership and regulatory bodies for their respective therapies and hold accredited registers of the Professional Standards Authority (Professional Standards Authority, nd), neither therapy has chartered status or protected title. Some practising acupuncturists and NTs are not members of a professional organisation, or may be members of organisations that do not hold accredited register status; they may have widely varying policies on issues such as safety, scope of practice, ethics, training/educational level, professional standards and extent of professional insurance (although it is not known what proportion of the practitioner population this represents). In designing Santé-AF, membership of either BAcC or BANT was used as an indicative "shorthand" for a given standard and scope of practice; if reconsidering practitioner eligibility criteria, a future trial may wish to weigh questions of professional standards and safety against its practitioner cohort's representativeness of real-world practitioner populations.

These parameters may not be easily reconciled. To illustrate: in a scenario where BAcC/BANT membership is not an eligibility criterion but participant safety remains a primary concern, a future trial should consider commissioning expert practitioners of both therapies (who would ideally also help to design training workshops and practitioner study manuals, and would continue as members of a Trial Steering Committee) to draw up a list of additional practitioner eligibility criteria and professional, ethical, safety and scope of practice requirements that may be applied via an extended version of the contractual mechanisms used by the feasibility study. However, this would lead to an increased recruitment and consent burden for practitioners, perhaps depressing practitioner recruitment or introducing Hawthorne effects and distorting routine practice; and such detailed requirements may introduce selection bias in the practitioner cohorts which defeats the pragmatic objective in any case.

Recommendation: For safety reasons, it is recommended that existing eligibility criteria of qualification level and membership eligibility are retained, and noted as a limitation in a future trial.

7.3 Objective 3: Participant retention

7.3.1 Feasibility of objective 3

The progression criterion for objective 3 measured the percentage of randomised participants retained at follow-up, with a threshold of ≥80% to align with the 20% margin allowed for attrition during sample size calculation. Santé-AF retained 83.3% (n=25) at follow-up, and by this threshold can be judged feasible.

This compares less favourably with median retention rates of 88% in large-scale trials published in NIHR journals and 89% in trials published in the UK Health Technology Assessment programme (Jacques et al., 2022; Walters et al., 2017). However, it compares favourably with feasibility studies in both acupuncture and nutrition. Bostrøm et al.'s feasibility study of acupuncture versus manual therapy for lateral epicondylitis (2019) retained 78.0% at a 12-week follow-up point. In a feasibility study of acupuncture for post-operative symptoms including AF, the retention rate over three months was 74.6% (Feingold et al., 2023); Jia et al.'s Chinese study of acupuncture for osteoarthritis of the knee retained 77.8% at a 16-week follow-up while a similar UK trial (White et al., 2016) achieved 77.0% retention at 14 weeks; a study of acupuncture for back pain in pregnancy retained 74.0% at eight weeks (Foster et al., 2016); and a study of acupuncture for overactive bladder retained 76.7% at 14 weeks (Hargreaves, Harding and Clarkson, 2021). For nutrition, a study of individualised nutrition for prevention of hospital readmission in geriatric patients (Cramon et al., 2021) achieved 66.6% retention at 60 days.

Although Santé-AF met its progression threshold for retention, the feasibility study findings suggest some changes that may improve retention in a future trial.

7.3.2 Differential loss to follow-up between groups

While the feasibility study achieved its global retention threshold, **Figure 7** shows that the NT group retained a smaller proportion of participants than the Acupuncture group (n=9 or 75.0%); and the Usual Care group retained a smaller proportion still (n=4 or 66.0%). Differential loss to follow-up poses a problem for the intention-to-treat (ITT) approach to data analysis that is standard practice in pragmatic trials (Welsing et al., 2017; Zwarenstein, 2017): as ITT analysis takes no account of between-groups differences that arise from participant-level protocol deviations, it may attenuate those differences (Tripepi et al., 2020). If a future trial encounters a large proportion of protocol deviations of this type, a secondary analysis may be added to the primary ITT analysis to study the effects of the intervention, perhaps using Complier Average Causal Effect (CACE) methods in preference to a "naïve" per-protocol analysis to avoid biases associated with non-compliance (Welsing et al., 2017; Gruber et al., 2014; Connell, 2009). It is also advisable to consider the

various reasons for increased attrition in the NT and Usual Care groups, and to mitigate these as far as possible.

Various possible reasons for differential loss to follow-up are discussed below, and suggestions made for mitigation.

7.3.2.i Online working for NTs

In the feasibility study, it is possible that participant 2/122/NT withdrew due to poor technology skills. A future trial choosing to maintain the online working of NTs, together with the recommendation to remove upper age eligibility criteria, may experience lower appointment or intervention adherence, and/or a higher rate of attrition in the NT group, possibly resulting in differential loss to follow-up which may introduce attrition bias (Rengerink et al., 2017; Akl et al., 2012). However, NTs' shift to exclusively online working at the start of the COVID-19 pandemic appears to have been superseded by working both online and in-person according to patient preference (British Association for Nutrition and Lifestyle Medicine, 2023). It would therefore appear feasible to stipulate (as an eligibility criterion) that NT practitioners offer choice to participants regarding online/in-person appointments (although as noted above, the offer of choice in any dimension would appear to influence treatment effects that may artificially inflate the effects of NT in comparison to both other groups in the trial).

Recommendation: A future trial should consider the benefits and disadvantages of NT practitioners offering both online and in-person appointments in relation to retention and preference effects.

7.3.2.ii Location of practitioners

Another issue giving rise to possible differential loss to follow-up may be the location of acupuncturists (and NTs, in the event that a future trial requires NTs to work in-person). One participant, randomised to the Acupuncture group, was unable to attend the intervention appointments but agreed to complete the follow-up assessment (**6.3.4**). While this is pragmatic in that it represents a real-world problem (Welsing et al., 2017), the participant's reasons for non-adherence suggest that, in a future trial, participants may be poorly adherent with regard to attendance if asked to attend logistically inconvenient appointments (Ee et al., 2018; Treweek, 2015) – especially in the Acupuncture group, which required eight appointments compared with NT's three, representing increased burden.

Recommendation: A future trial should recruit practitioners local to the catchment area of PICs. It may also be advisable to consider some of the attributes found valuable by participants in the NIHR

Participation in Research (PRES) studies, including car parking and appointment convenience (National Institute for Health and Care Research, 2022).

7.3.3 Follow-up period

The single follow-up for Santé-AF was positioned at the end of treatment (EOT), approximately three months from start of intervention; no longer follow-up was possible, due to the delays caused by COVID-19. This represents a significant limitation of this feasibility study: it would have been helpful for a future trial to understand loss to follow-up rates over a longer period for this population undergoing these interventions. It is also known that shorter follow-up at feasibility stage may lead to over-estimation of retention rates (Avery et al., 2017). Trials with too short a follow-up also produce uncertainties regarding whether short-term effects persist, and may not detect all adverse responses occurring after the follow-up period (Hemkens, 2018); and a longer follow-up would also allow a real-world representation of treatment cost-benefit for both therapies to be included in the investigation (Bengey et al., 2023).

Additionally, in a pragmatic trial investigating two complex interventions, heterogeneity of participant characteristics and other treatment-related variables suggests that longer follow-ups are needed to represent true effects of interventions (Patsopoulos, 2011; MacPherson, 2004). There is strong evidence to show that the treatment effects of acupuncture in particular are maintained with only small decreases over durations up to 12 months (Liao et al., 2020; Vickers et al., 2018; MacPherson et al., 2017b; Thomas et al., 2006); and while the longitudinal effects of NT have not been investigated, the nature of the therapy – in providing tools and approaches enabling patients to maintain a regime beyond the end of treatment course – could be hypothesised as amenable to a longer follow-up than the three months achievable by this feasibility study.

Recommendation: A longer follow-up is recommended for a future trial in addition to the current three-month EOT follow-up. However, it is recognised that there is significant uncertainty regarding feasibility as this was not a subject of investigation by this study. If a longer follow-up is incorporated, a future trial should adopt a more conservative estimate of retention rates than those arising from Santé-AF retention data (Herbert, Kasza and Bø, 2018). A longer follow-up may also require extra resources to maintain retention rates (Oetzmann et al., 2022).

7.4 Objective 4: Intervention acceptability

7.4.1 Feasibility of objective 4

Objective 4 assessed intervention acceptability by analysing participants' report of group allocation satisfaction, and participants' report of the overall acceptability of their intervention. Acceptability was defined following Sekhon, Cartwright and Francis's proposal of "a multi-faceted construct that reflects the extent to which people… receiving a healthcare intervention consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention" (2017, p.1), and further informed by dimensions of acceptability defined by (Gooding et al., 2018).

While the sample size of the feasibility study was not sufficient to demonstrate robust effects, participants' experience of the study's interventions would appear to compare favourably with patients' general experience of conventional treatments, particularly medication (**2.1.8.v**).

Both progression thresholds were met for intervention acceptability. However, two issues emerged during the feasibility study that nuance these thresholds. These are discussed below.

7.4.2 Treatment expectation

Patients' expectations of treatment – beliefs about treatment-related outcomes (El-Haddad, Hegazi and Hu, 2020) – are a central component of placebo response, and have been shown to affect outcomes with direct correlations in both directions (i.e., positive expectations of treatment are associated with positive outcomes, and negative expectations with negative outcomes) (Uebelacker et al., 2018; Eklund et al., 2019; Bishop et al., 2015; Prady et al., 2015; Barker Bausell et al., 2005; Moffett et al., 2005; Kalauokalani et al., 2001). By contrast, a systematic review found that of nine studies of acupuncture, only five detected statistically significant effects of expectancy on outcomes (Colagiuri and Smith, 2012). This aligned with the findings of Sherman et al. (2010) that a positive predisposition towards the treatment was not predictive of improved outcomes amongst 477 participants in a trial of acupuncture for back pain; and the findings of Qi et al. (2022), who found no conclusive evidence for an association between expectancy and treatment effect in an n=138 analysis of participants receiving acupuncture for postprandial distress syndrome.

A future trial may choose to examine treatment expectations for AF patients in relation to acupuncture and NT, as a nested sub-study. Accounting for treatment expectations would be particularly important in the context of a preference trial design as discussed above, but would still be needed in a future trial that did not adopt a preference design, to include as a covariate in analyses of effect.

To test the feasibility of data collection for an analysis of treatment expectation in relation to outcomes, Santé-AF used a simple SMS poll with three categories of treatment expectation in relation to AF symptoms only, i.e., not HRQoL (get worse; stay about the same; improve). This method was used for ease of communication and mitigation of participant burden, and was able to collect responses from n=28 (97.0%) of participants.

The literature shows that a wide variety of instruments and methods has been used to measure expectations in studies of interventions; variety has contributed to a lack of comparability and possibly also heterogeneity of findings (Barth et al., 2019). A future trial may prefer to use a validated instrument that is neither disease- nor intervention-specific, such as the Treatment Expectation Questionnaire (TEX-Q) (Shedden-Mora et al., 2023), the Expectation for Treatment Scale (ETS) (Barth et al., 2019) or the EXPECT questionnaire (Jones et al., 2016); however, a questionnaire would be more time-consuming than the methods used by this feasibility study, and would therefore add to participant burden.

All these questionnaires are designed for application at pre-intervention stage, but two studies of acupuncture for migraine found that post-treatment expectations (of longer-term benefit) were more accurately predictive of longitudinal treatment response than pre-treatment expectations (Pokladnikova et al., 2019; Zheng et al., 2015). A future trial accepting the recommendation for a longitudinal follow-up may choose to investigate this hypothesis in this population by collecting post-treatment responses in addition to baseline responses, although this may require the design of a suitable instrument and would require extra trial resources.

Recommendation: A future trial should consider collecting data on treatment expectation applied at baseline in addition to post-treatment, perhaps using a validated instrument if this does not add to participant burden unnecessarily.

7.4.3 Adherence (participants)

In the feasibility study, participant adherence to interventions was measured quantitatively in an exploratory analysis of attendance at appointments. In these terms, Santé-AF participants' adherence compared favourably with other broadly comparable feasibility studies in acupuncture and nutrition. For instance, a study of acupuncture and manual therapy for lateral epicondylitis (Bostrøm et al., 2019) found that of a maximum eight treatments, acupuncture participants attended a mean number of 3.9 sessions (49.0%), compared with Santé-AF's mean of 7.1 (88.6%). Similarly, in a study of acupuncture for post-operative symptoms including AF, the attendance rate was 83.0% (Feingold et al., 2023). A Chinese study of acupuncture for knee osteoarthritis expected participants to receive at least ten treatment sessions, achieving 100% adherence at that level (Jia et al., 2020a); similarly, Lee et al.'s trial of acupuncture for AF symptoms found that patients were

highly adherent (Lee et al., 2017). The cultural acceptance of acupuncture in China and Korea may account for this high level of compliance (Cao et al., 2020; Zheng, Chang and Chen, 2014). Cramon et al.'s 2021 study of individualised nutrition for prevention of hospital readmission in geriatric patients also achieved 100% compliance with the two home visits within 60 days that comprised the intervention.

It is recognised that appointment attendance is not always a close proxy for adherence (Kline et al., 2018; Ogedegbe, Schoenthaler and Fernandez, 2007). For Santé-AF, attendance at appointments could be regarded as one of two measures of adherence, with the second being adherence to self-care/lifestyle advice. As discussed in an earlier chapter (**2.1.7.i**), the use of risk factor management (RFM) has been shown to be effective in attenuating symptoms and improving HRQoL, and this element of both interventions was expected to play some part in treatment effects. Research investigating adherence (usually to medication) in cardiac patients is a growing field (Kumar, Mohammadnezhad and May, 2021; Chung et al., 2020; Cabellos-García et al., 2018), but very little work to date has considered adherence to self-care/lifestyle advice and the factors affecting this in AF patients; such research may be considered timely as AF management strategies move towards self-management of modifiable risk factors.

In the feasibility study log books, practitioners were asked to describe their perception of participants' adherence to self-care/lifestyle advice (**Appendix A**, Practitioner documents section); for participants themselves, the follow-up questionnaire asked participants how *easy* it was to follow their self-care/lifestyle advice, measured on an ordinal scale, with the interview subset also exploring this qualitatively. Participants' own estimate of *how much* or *how far* they actually did adopt self-care/lifestyle advice (and why/why not) would add useful triangulation, particularly when baseline and EOT measurements are compared with a longitudinal follow-up (O'Reilly et al., 2021). Self-care/lifestyle advice adherence could therefore be more closely followed up in a future trial to explore any associations with longitudinal outcomes, as has been previously hypothesised in the literature (Gawałko et al., 2020; Nouwen et al., 2011).

Recommendation: A future trial should incorporate a quantitative and qualitative exploration of participants' adherence to self-care/lifestyle advice (including usual care participants) to investigate the relationship between adherence and outcomes along with reasons for adherence/non-adherence, across EOT and a longitudinal follow-up. This decision should be made in the context of specific issues with NT adherence in **7.1.2 above** and **7.8.5.iv below**; and in the additional context of intervention fidelity discussed in **7.7.3.i below**.

7.5 Objective 5: Assessment acceptability

7.5.1 Feasibility of objective 5

The feasibility of objective 5 (the acceptability of assessments to participants) was assessed on two progression criteria. The first of these assessed the completeness of data returned for the four main outcomes, with a progression threshold of ≥80% completeness. Santé-AF participants returned 90.0% of data, and the objective was judged feasible. This compares well with the completeness of data returned by the participants in Hargreaves, Harding and Clarkson's feasibility study of acupuncture for overactive bladder (2021), in which participants returned 76.7% of the full dataset (three validated outcome measures).

The second criterion considered the acceptability of assessments, setting a feasibility threshold of ≥90% participants reporting an acceptability score of 1–3 on a 7-point scale (lower numbers = greater acceptability). This threshold was not met, as only 88.0% of feasibility study participants rated the assessments at 1–3 (two percentage points less than the threshold). However, one of the three participants giving an acceptability score of 4–7 was 2/163/A who may have misunderstood the question scale (**6.5.2.i**). Had this participant recorded a rating of 3 ("somewhat acceptable"), which may cautiously be assumed to accord with the qualitative comment, the percentage of participants rating assessment acceptability at 1–3 would have been 92.0%, and this progression threshold would have been exceeded by two percentage points. It is therefore suggested that this progression threshold should be regarded as having been met, with no adjustments required for a future trial. A discussion of "question flips" can be found in **7.5.3.iii below**.

While both progression thresholds were met, the study revealed additional findings that a future trial may wish to consider, to increase acceptability of assessments for participants.

7.5.2 Online assessments

Santé-AF demonstrated that it was feasible to carry out assessments online during the COVID-19 pandemic, but the process and its outputs were not optimal. While participants generally accepted the need to work online, a high proportion expressed preferences for assessments to be carried out in-person (**6.5.2.ii**). The process was also associated with burden for the researcher which lengthened overall timescales; it also increased study costs considerably, and may not have produced accurate data from participants (anthropometric measurements, CardioSTAT® data, and in several cases questionnaire and interview data) (**6.5.2.iii**).

Recommendation: It is recommended that a future trial should not use online methods of assessing participants.

7.5.3 Reducing participant burden in assessments

Santé-AF collected a range of quantitative data to understand the effects of the interventions on quantitative measures; qualitative data was also collected to detect individually meaningful change that may be more amenable to qualitative expression.

The feasibility study's participant-related data collection was carried out centrally by the researcher, rather than by practitioners during routine appointments. In terms of pragmatism, this was a "rather explanatory" approach, and also increased burden for participants; some participants found assessments burdensome. While assessment acceptability met its feasibility threshold, the study made findings that, if adopted in a future trial, would mitigate participant burden.

Recommendation: A future trial should retain the use of qualitative data to detect and understand individually meaningful change, but should also consider its primary and secondary research questions to reduce participant burden in data collection, balancing this with the value for money required by funders (Hind et al., 2017).

7.5.3.i Reducing burden in the pre-consent screening call

A specific aspect of Santé-AF found to be burdensome by participants was the pre-consent screening call. As noted, this was redesigned to include a full check of all eligibility criteria (**5.7.1.iii**) and became much longer as a result. Simplified eligibility criteria (**7.2.1** and **7.2.1.i**) would automatically reduce the burden of the screening call for participants. In addition, the complex eligibility criteria of the feasibility study may have contributed to one of the safety-related incidents (i.e., PIC errors in search/screening); simplification of eligibility criteria would render similar incidents less likely.

7.5.3.ii Data collection by practitioners

The ultimate pragmatism in trial data collection is the collection of registry data without direct participant involvement (Giraudeau et al., 2022; Chan et al., 2021; Loudon et al., 2015). Unfortunately, ongoing reassessment of AF in primary care is limited (Charlesworth and Palumbo, 2023) leading to limited information available via primary care databases. An alternative may be to require practitioners to collect data (Meinecke et al., 2017).

Practitioners routinely collect some of the data required by a future trial. For instance, NTs collect anthropometric data for clients pursuing weight loss; acupuncturists collect data on pain levels, self-care and mental health; all practitioners routinely collect data on medical history including the symptoms and conventional treatment for presenting conditions and comorbidities; details of current diet, smoking status, alcohol intake; and medications and adherence to self-care/lifestyle advice. All are regularly updated as treatment progresses. A future trial may therefore find it

practical and pragmatic to require practitioners to collect this data from participants; this would reduce the time required for the overall assessment.

Other data required by a future trial is not part of practitioners' routine data collection (such as demographic data and healthcare resource usage), and a requirement for practitioners to collect this would deviate from routine practice. It may also distort the patient-practitioner relationship, which may in turn compromise the quality of treatment in addition to making it less representative of that delivered in real-world contexts (Meinecke et al., 2017).

Additionally, the quality of some types of data collected by practitioners may be sub-optimal and/or introduce bias. Where measures are self-reported, there is a possibility of introducing reporting bias (also known as "obsequiousness bias" (Cook, 2010)) due to "demand characteristics" where participants report what they consider to be favourable outcomes, influenced by the patient-practitioner relationship (McCambridge, Kypri and Elbourne, 2014; McCambridge, Witton and Elbourne, 2014; McCambridge, De Bruin and Witton, 2012). This type of bias may affect interviews, questionnaires, and the reporting of symptoms in the symptom diary, particularly at follow-up where participants are asked to reflect on the quality and effects of their therapy. Practitioner measurement also introduces the possibility of assessor bias, as practitioners by nature cannot be blinded to treatment allocation.

Other problems posed by practitioner data collection are practical in nature:

1. Separate arrangements would need to be made for Usual Care participants' assessments, as these cannot be incorporated within intervention appointments.
2. During the feasibility study, NTs delivered interventions online; if this is continued in a future trial, NTs would be required to hold at least the first and final consultations in-person to carry out assessments.
3. It is good practice to ensure that all those involved in delivering a study are trained appropriately (NHS Health Research Authority, 2017). To train practitioners in data collection techniques, including fitting the CardioSTAT® and anthropometric measurement techniques, would require ≈ one day of each practitioner's time, requiring recompense amounting to approximately £400–£600 per practitioner. In addition, Santé-AF practitioners commented during the pre-trial training workshops that the requirement to do what they regarded as a substantial amount of extra training would have deterred them from participating.
4. Practitioners would require recompense for carrying out assessments. If not carrying out interviews or administering questionnaires, assessments would take an average 24

minutes. Participants would be required to give extra time to appointments at the beginning and end of their intervention.

5. Practitioners should be provided with standardised equipment, including medical weighing scales and tape measure, a stadiometer and a blood pressure monitor; all should ideally be recalibrated regularly.
6. A longitudinal follow-up would need to make special arrangements for all participants to be assessed.

Recommendation: A future trial should consider requiring practitioners to collect some measurements and self-reported data, recognising the possibility of participant bias in the latter as a limitation of the trial. Questionnaires and interviews should be conducted centrally to reduce bias, and CardioSTAT® monitors (if retained) should be fitted by a trained professional to help reduce noise and increase analysable data proportions (MacFarlane, 2023); this may be a practitioner or trial personnel.

7.5.3.iii Questionnaire burden

Although the response rate of the Santé-AF questionnaires was high (**Table 30**), it is possible that the baseline and follow-up questionnaires contributed to participant burden (**6.5.2.ii**). Survey fatigue related to burden is a well-documented phenomenon that reduces participant thoughtfulness and accuracy when responding to surveys (De Koning et al., 2021; O'Reilly-Shah, 2017), and to that extent reduces the validity of questionnaire data. The numbers of participants disliking the follow-up questionnaire in Santé-AF represented a five-fold increase over the numbers disliking the baseline questionnaire (**Table 31**), suggesting that the follow-up questionnaire may have the potential to increase item non-response and/or loss to follow-up, both of which may introduce bias to a future trial. The remedy for questionnaire survey fatigue may be a reduction in questionnaire length (Edwards, 2010), but other research suggests that questionnaire content and design, including visual appearance, may be an alternative or additional predictor of fatigue/adherence (Rolstad, Adler and Rydén, 2011).

In a future trial, questionnaires would automatically reduce in length, as questions on feasibility would not appear (baseline = 11 questions (14.5%); follow-up = 14 questions (15.4%)). Additionally, unless a future trial took place under COVID-19 conditions, questions regarding participants' vaccination status and attitudes to infection risk from the study may also be removed (baseline = four questions (5.3%); follow-up = four questions (4.4%)).

A specific issue for the Santé-AF questionnaires was the use of reverse wording in the follow-up questionnaire. All Likert-scale questions were set out in ascending numerical order, but questions were forward- or reverse-worded according to the item being rated (i.e., AF-related symptoms

where lower numbers indicated lower levels of symptoms; study acceptability where lower numbers indicated greater acceptability). Research suggests that "question flips" of this kind confuse participants and lead to erroneous answers (Sonderen, Sanderman and Coyne, 2013), and that standard question formats increase reliability (Boynton and Greenhalgh, 2004). The feasibility study revealed clear evidence that one participant answered some "flipped" questions erroneously (**6.7.1.i**).

A final content-related issue for the Santé-AF questionnaires, which may have contributed to burden and also to missing data, was the absence of a "none of the above" option for several of the multiple-choice questions. Participants frequently asked questions regarding this while completing questionnaires during assessments, and were advised to write "n/a" or "none of the above" if so; however, not all participants asked about this.

Recommendation: A future trial should reduce questionnaire burden by removing feasibility questions and COVID-19 questions; add a "none of the above" option where appropriate; and consider standardising question wording. The latter two recommendations would not apply to the questionnaire elements that are validated (i.e., EQ-5D and AFEQT questionnaires).

7.6 Objective 6: CardioSTAT® utility

7.6.1 Feasibility of objective 6

The utility of the CardioSTAT® ECG monitor was measured by two criteria, both defined in terms of the monitor's role in the feasibility of a future trial.

The first criterion was the agreement between symptom diary and monitor, measured as the number of episodes recorded by each. It was not possible to determine the agreement between the monitor data and some/all AF episodes recorded in the symptom diary due to noise (**6.6.1**). This analysis was abandoned, and the feasibility criterion was not applied.

The second criterion concerned participants' report of the monitor's influence on their decision to participate and remain in the study. This criterion did not meet its progression threshold (**Table 34**). Applying the ADePT criteria (Bugge et al., 2013) suggested that adjustment to trial parameters may help in meeting this threshold in a future trial, but the proposal that trial parameters should be adjusted to increase the influence of the monitor is not credible; positioning this domain as a progression threshold was therefore judged to be inappropriate, and the threshold was not applied.

Nonetheless, it was still of use to a future trial to conduct this analysis without applying a progression threshold. The analysis allowed an understanding of whether, and to what extent, the monitor represented an incentive to take part and remain in the study, so that a future trial may take account of any significant effect on participation/retention associated with removing or retaining the monitor. Analysis suggested that the monitor appeared to be a proportionate incentive to participate and remain in the study, and its removal from a future trial would not pose substantial challenges to recruitment or retention (**6.6.3**).

7.6.2 CardioSTAT® versus symptom diary

Inclusion criterion 4 (INC4) required Santé-AF participants to have self-detectable AF that was paroxysmal (defined as "episodes of AF that stop within seven days, usually within 48 hours, without any treatment" (National Institute for Health and Care Excellence, 2021)) with a minimum weekly frequency. This criterion was defined because:

- The study tested the feasibility of the symptom diary in recording symptoms. Completing the diary required participants to be aware of onset/offset with frequency being, on average, at least once per seven-day period;
- Symptoms were thought to be identical with AF – i.e., symptoms such as palpitations, dyspnoea, fatigue and chest pain were taken to indicate active AF.

However, the conflation of symptoms with active AF was an error. A study of AF patients with pacemakers found that symptoms were often not associated with pacemaker-verified episodes (Strickberger et al., 2005); as Rienstra et al. wrote in 2012, "the simple awareness of symptoms is not a good discriminator of the presence or absence, nor the severity of the arrhythmia" (p.2937). This was further confirmed with the study's consultant cardiologist (Charlesworth and Gupta, 2023).

On the assumption that symptoms were indicative of actual AF, a feasibility domain was added to investigate agreement between symptoms as recorded in the self-report diary and AF as recorded by the CardioSTAT® monitor. This analysis was found to be unworkable for a number of reasons including the percentage of CardioSTAT® non-analysable data, but was also conceptually unworkable due to the erroneous conflation of symptoms with actual AF. This is discussed below.

7.6.2.i Perceptibility of symptoms

Irrespective of whether they were understood to indicate active AF, the symptoms of Santé-AF participants may not have been noticeable enough to record. Recent research has found that the experience of symptoms is highly heterogeneous across the AF population (Wilson et al., 2021, 2020; Streur, 2019). Post-study conversations with the study's consultant cardiologist and a PIC GP

revealed their clinical observation that some patients do not feel symptoms acutely or even at all, particularly if they are older (Charlesworth and Gupta, 2023; Charlesworth and Palumbo, 2023). This observation is congruent with recent speculation in the clinical literature that atrial myopathy may cause gradual changes in atrial substrate over time, meaning that AF symptoms onset incrementally and are therefore not distinct or noticeable for a proportion of patients (**2.1.4.i**).

This imperceptibility of symptoms was observed in Santé-AF participants. At screening call stage, all participants reported conforming to INC4 (i.e., their AF was paroxysmal, perceptible by them, and of at least weekly frequency); but according to comments made to practitioners during appointments (**6.7.5**), some participants in fact did not notice their symptoms. These participants may arguably be regarded as having been randomised in error. This difficulty has been experienced in other trials for symptoms in atrial fibrillation, notably in a study by Lee et al. (2021) which made the ancillary finding that participants who were aware of their AF symptoms reported a more positive response to acupuncture; the authors recommended narrowing the inclusion criteria to include only patients with perceptible symptoms.

For the n=10 participants who were allocated to both wear the CardioSTAT® monitor and complete the diary (n=9 at follow-up), **Table 33** showed very little correspondence between the two: participants perceived symptoms where no AF existed, and vice versa. The symptom diaries of three (33.3%) showed an average increase of 2.9% symptoms between baseline and follow-up (250.9 minutes ± 199.3 minutes); comparing this with the CardioSTAT® data shows that actual AF for two of these three remained at 100.0% of analysable data between baseline and follow-up while the third decreased from 1.8% to 1.1% of analysable data. Similarly, of the n=6 (66.6%) participants whose symptom diaries recorded a decrease in perceived symptoms (average 0.8% (362.1 minutes ± 64.1 minutes)) between baseline and follow-up, the corresponding CardioSTAT® data indicates that the AF of only one participant had actually decreased (2/964/NT) while the monitors of another four recorded 100% AF during analysable data periods at both measurement points. (The sixth participant with perceived decrease in symptoms was 1/884/UC, whose case is described below.) This suggests that, in this subset of Santé-AF participants, perceived symptoms were not necessarily indicative of active AF, and active AF did not necessarily give rise to perceptible symptoms; this supports the findings of Wilson et al. (2020) and Streur (2019) along with the observations of the study's clinical colleagues, above.

For Santé-AF participants, the percentage of non-analysable data was as high as 86.4% (average 23.0% ± 27.7%); discussions with the manufacturer suggest that the high proportion of noise may have been at least partly due to inexpert self-fitting of the monitor during the COVID-19 pandemic (MacFarlane, 2023).

The symptom diary may have been subject to inaccuracy due to a range of factors including questionnaire fatigue, emotional responses to symptoms, and inconvenience of recording; some obsequiousness bias may also have been present if (despite repeated assurances) participants were not confident that their diaries would not be shared with practitioners (Cook, 2010). Additionally, some participants may have actively disregarded symptoms, and those wearing the CardioSTAT® may have relied on the diary to record symptoms (**6.6.1**).

Despite this level of potential inaccuracy, this study has detected and clarified a useful distinction between perceived symptoms and the active presence of AF ("active AF"). The investigational studies literature relies largely on participant self-report over ECG monitoring (Hindricks et al., 2020) and therefore often reports what this study has defined as "perceived symptoms". In general, as discussed in **2.1.6.i above**, perceived symptoms are somewhat associated with HRQoL; a decrease in perceived symptoms may therefore benefit HRQoL whether or not it corresponds to a reduction in active AF (Abu et al., 2022). However, if the upper age limit is removed in a future trial and a greater number of older participants is recruited, it is possible that perceived symptoms may not substantially change between baseline and any follow-ups, due to potentially reduced symptom perception in older people with AF; although as discussed in **2.1.6.i above**, this does not preclude an independent improvement in HRQoL.

Recommendation: A future trial should regard perceived symptoms as independent of active AF. Therefore the self-report symptom diary and the CardioSTAT® may both be retained, with the former as a measure of participants' symptom perceptions and the latter as a record of active AF. This would allow removal of the eligibility stipulation regarding participants' "awareness of AF", enabling participants to regard the symptom diary simply as a measure of perceived symptoms and so allowing a future trial's participants to reflect the AF population more closely.

7.6.2.ii Cost versus benefit of the CardioSTAT® monitor in a future trial

As shown in **Table 33**, the main feasibility issue associated with the use of the CardioSTAT® monitor in a future trial is the absence of a consistent unit to be extracted from the data (**6.6.1**) due to the randomly-varying percentage of analysable data generated by each monitor. This suggests that between-participants comparisons on a continuous outcome are not possible using CardioSTAT® data. In clinical practice, the monitor is used to detect AF presence/absence over the analysable data period; however, the feasibility study data suggests that a binary outcome is not realistic for the interventions investigated, and equally, time-to-event during a seven-day period is not an appropriate measurement either. A second feasibility issue is the monitor's cost (**6.6**), which represents a significant financial burden for a future trial.

Since the endpoint of interest for a future trial is the mean difference between each intervention group and usual care at follow-up, the CardioSTAT® may be discarded at baseline, but applied at one or both follow-ups (if the recommendation to incorporate a longitudinal follow-up is accepted). This would disallow the use of CardioSTAT® data as a covariate in the endpoint analysis, but given the degree of within-participant variations shown in the feasibility data it is in any case questionable whether the presence or degree of AF at baseline would predict this variable's value at follow-up.

If it is reasonable for a future trial to assume that (i) sample size and randomisation have accounted for between-participant differences at baseline (and by the same token, within-participant differences are similarly balanced between groups at follow-up); and (ii) there are no significant differences in the average proportion of analysable CardioSTAT® data between groups (as these differences are random between participants in any case and there is no other reason why a group-specific reason for differences should exist) (Roberts and Torgerson, 1999), the group means of active AF recorded by the CardioSTAT® may be a useful exploratory analysis at follow-up.

Alternatively, given the cost and data difficulties, the CardioSTAT® may be regarded as not being a useful outcome measure in a future trial. This would leave three self-reported outcome measures in a future trial, which may be considered to contradict good practice as recommended by the European Medicines Agency (2014) in combining subjective and objective measures; it may also confer bias by using only subjective outcome measures in a trial where blinding of participants is not possible (Wood et al., 2008). However, the expense of the monitor combined with its limited utility may restrict its benefit.

Recommendation: A future trial should weigh the benefits and disadvantages of the CardioSTAT® monitor, as discussed in this section, to take a decision on its use. If used, its application at one or both follow-ups, but not at baseline, may help restrict costs.

7.7 Objective 7: Experience of study participation

7.7.1 Feasibility of objective 7

A progression threshold was set for objective 7 – the overall experience of study participation – at 75% of participants rating participation acceptability at 1–3 on a 7-point scale (where lower numbers = greater acceptability). 96% of Santé-AF participants rated overall participation at 1–3; this aspect of a future trial can be judged feasible. Some findings of the study present opportunities to increase participation acceptability, discussed below.

7.7.1.i Study documentation

Many participants disliked engaging with the study documentation, feeling the participant information sheet in particular to be too long, and the consent form to require too much input. Both issues would be automatically mitigated if earlier recommendations are accepted to widen eligibility criteria.

7.7.1.ii Effect of the COVID-19 pandemic

The COVID-19 pandemic appears to have negatively affected the feasibility of the study in several dimensions, including decreasing PICs' willingness to participate; decreasing pragmatism and depressing recruitment by adding extra eligibility criteria; decreasing acceptability of assessments by requiring online working; and depressing quality and integrity of data collected due to assessments being held online. Additional negative feasibility effects observed during the study due to COVID-19 included an increase in research costs and researcher burden, and delays in the scheduling of study assessments.

Other dimensions of feasibility were only slightly or not at all affected by the COVID-19 pandemic, including practitioners' willingness to participate; appointment attendance; acceptability of intervention for NT participants arising from online working; participants' general experience of participation, including perception of COVID-19 risk as a result of taking part; and practitioners' general experience of trial participation.

Other possible effects of COVID-19 on feasibility are unclear due to lack of data and must remain speculative. These include willingness to participate at pre-consent stage; and participant withdrawal due to contracting COVID-19 or possibly due to poor technology skills related to working online.

Unless a future trial took place under similar pandemic conditions, the removal of COVID-related modifications is likely to increase feasibility.

7.7.2 Practitioners' experience of study participation

For practitioners' experience of study participation, no progression criteria were set in the feasibility study; but practitioners' experience is an important element of feasibility and it is recommended that future feasibility studies delivering interventions via private sector providers should set progression criteria for acceptability.

Analyses of practitioner experience in the feasibility study suggest that some aspects of practitioner process may be optimised to increase the trial's attractiveness to practitioners. These are discussed below.

7.7.2.i Process optimisation relating to practitioners

The feasibility study revealed several aspects that could be changed to increase the attractiveness of a future trial to practitioners.

Recommendation: In view of the holistic nature of the interventions, a future trial's log book should be amended to offer more opportunities for (optional) free-text comment, enabling practitioners to nuance the rationale of their work (**6.7.3**).

Recommendation: A future trial should retain the feasibility study's practitioner communications channels and repositories – email, website with document repository, text, phone and WhatsApp groups. WhatsApp groups should be presented as being for study communications only, with social chat minimised. Material discussed in WhatsApp groups should be consented for use in a future trial's analyses in the practitioners' legal agreements (**6.7.3**).

Recommendation: Peer supervision groups were liked by all practitioners as a means of support and building a sense of community. While free disclosure and discussion would be poorly served by regarding these groups as a data collection opportunity in a future trial, the noting of themes and issues for future discussion in practitioner exit interviews worked well and helped to inform the researcher's understanding of several important points including the nature of usual practice and any compliance tensions, safety, and typical participant-facing issues. Groups should therefore be included in a future trial (with perhaps more than one iteration during the intervention period, depending on period duration). Remuneration may be offered, to increase attendance; and a future trial should consider holding groups online to allow attendance without travel. Researcher presence should mitigate the risk of groups presenting cross-practitioner contamination that may distort routine practice.

Recommendation: Some practitioners, particularly acupuncturists, found some difficulty with delayed payments for treatments delivered. A future trial should expedite fee payments to practitioners, to encourage recruitment and retention (**6.7.3**).

7.7.3 Intervention fidelity

This section discusses the ways in which interventions were delivered, and the extent to which trial practice reflected real-world practice. This largely concerns the therapies' scope of practice, but two logistical issues discovered during the feasibility study are discussed in addition.

Practitioners appear to have largely adhered to the required scope of practice, and the feasibility study demonstrated feasibility of collecting data at individual consultation/treatment level that would, if analysed, allow a full understanding of the interventions delivered in a future trial. (No such analysis was carried out for this study as it was not relevant to feasibility.)

The feasibility study scope of practice was restricted by study budget and the requirements of the approving ethics committee. While all restrictions were thought to be workable and were justified at study design stage, experience from the feasibility study gave a real-world understanding of how these restrictions might contribute to a number of fidelity issues for a future trial, discussed below.

7.7.3.i Self-care/lifestyle advice

No self-care/lifestyle advice was given by one of the six practitioners (an acupuncturist). This practitioner felt her individual participants' TCM diagnosis contraindicated such advice, but also discussed a personal conviction that self-care/lifestyle advice as defined by the study was generally not indicated for most patients (**6.7.5**). This practitioner's views may represent a section of the acupuncturists' community: while older literature positions self-care/lifestyle advice as integral to acupuncture consultations (Evans et al., 2011; Eckersley et al., 2009), more recent research has found that acupuncturists now exercise more personal preference, particularly where patient-practitioner relationships are weaker, or in the context of more acute conditions (Pinto et al., 2022). This suggests that a future trial's inclusion of acupuncturists who do not offer self-care/lifestyle advice would be a pragmatic reflection of routine care. Notwithstanding, if a future trial wishes to focus on adherence to self-care/lifestyle advice as a possible factor influencing longitudinal effects (see **7.3.3** for a discussion of this point) it is clearly important that all practitioners are giving such advice.

Recommendation: A future trial should consider the balance between a pragmatic reflection of real-world acupuncture and a wish to study the association between self-care/lifestyle advice and treatment outcomes. If necessary, a practitioner inclusion criterion concerning willingness to give self-care/lifestyle advice could be added, with exceptions being considered a protocol deviation.

7.7.3.ii Referral of participants

Three practitioners wished to refer onwards to other complementary therapists, but were under the misapprehension that this was not allowed in the study. It appears that practitioners confused *referral* with *suggestions for adjunctive therapy;* in referral, patients are referred onwards and discontinue their current therapy, whereas a suggestion for adjunctive therapy is usually proposed alongside the current therapy. Suggestions of this kind, sensitive to participants' resources (time, money, emotional and logistical capacities), would have been reflective of routine practice and therefore acceptable in the study context.

Recommendation: A future trial should emphasise this point to practitioners, and practitioner study manuals should be altered to reflect this.

7.7.3.iii Supplementation (NT)

The third issue concerned two NTs' feelings of professional and ethical discomfort regarding the inability to recommend supplements (**6.7.5**). It is clearly undesirable (perhaps unethical) to place legally contracted practitioners in positions where they feel ethically compromised; this may affect willingness to participate or cause attrition, in addition to the effect on participants' welfare. The potential for such issues may be greater in a trial of holistic therapies, where therapeutic attention is often directed to a number of symptoms or conditions in addition to the condition under investigation; additionally, for a typically multimorbid condition such as AF with complex interlocking effects refracting between AF and comorbidities, fewer restrictions in therapeutic armoury may be especially advised.

For the study's NTs, the restriction on supplementation was initially made because funds did not allow the provision of supplements to participants, and it was judged unethical for participants to fund their own supplements. However, comments made by the approving REC suggested that even had the study been able to fund the provision of supplements to NT participants, supplements may still not have been permitted (**6.8.2**) as the REC appeared not to accept proof of NTs' training in avoiding the recommendation of supplements that would conflict with existing medication. This inference is somewhat speculative, and may differ in the case of a future trial that may apply to a different REC. In any case, the prohibition on supplementation did not avoid placing some cost burden on NT participants; see **7.8.5.iv** for a discussion of this point in the context of intervention harms.

In general, restrictions in the scope of routine practice could be considered to affect a trial's level of pragmatism; and for NT, some of the strongest evidence for AF treatment/prevention is in the area of supplementation (Ding et al., 2023; Huh and Jo, 2023; Lakkireddy, 2020; Parsi et al., 2018; Ali-Hassan-Sayegh et al., 2014). Therefore in routine practice NTs are likely to recommend supplementation as a component of treatment for AF. A prohibition on supplements may therefore render Santé-AF's restricted scope of NT unrepresentative of routine practice and affect confidence in the generalisability of a future trial's results to a wider real-world context, in addition to placing practitioners in challenging ethical situations.

Recommendation: A future trial should consider lifting the prohibition on supplementation for the NT group.

7.7.3.iv Delivery window

Three practitioners commented that the overall window of intervention delivery was too short to reflect routine practice (**6.7.5**), and that a longer window would not only more accurately reflect the interventions as delivered in the real world, but also potentially benefit participants' confidence and

self-efficacy. Greater flexibility regarding delivery window may lengthen timescales and possibly add to a future trial's parameter volatility (for instance, if final appointments are rescheduled at short notice this may require EOT assessment to be rescheduled likewise), but this may be considered a worthwhile balance in terms of pragmatism and benefit to participants.

Recommendation: A future trial should extend the overall window for intervention delivery in discussion with practitioners.

7.7.3.v Delays in scheduling appointments

All practitioners delivering interventions for Santé-AF were running busy clinics into which study participants had to be fitted. This had the effect of delaying participants' start-of-intervention after baseline assessment. The delays and their reasons are usual in routine practice and therefore reflected real-world practice, but may have contributed to measurement error in the active treatment groups (Kluzek, Dean and Wartolowska, 2022).

Recommendation: A future trial should consider adopting a different sequence of enrolment, as follows:

1. Randomise participant on receipt of valid consent;
2. Notify participant of group allocation. If in active intervention group, notify practitioner allocation and encourage first appointment contact;
3. Require practitioners to notify study centre of agreed date of first appointment, then schedule participants' baseline assessments (intervention groups only) to take place no less than eight days preceding start of treatment (to allow for post-assessment completion of the seven-day CardioSTAT® and symptom diary). Usual Care participants can be assessed immediately.

This approach would minimise measurement error while preserving a strong element of routine practice around appointment scheduling.

7.7.3.vi Effect of the pandemic on intervention fidelity (practitioners' perspective)

Asked whether the COVID-19 pandemic had affected intervention delivery, practitioners responded that they were fully accustomed to the changes required by the pandemic. Acupuncturists worked to a COVID-secure guideline (British Acupuncture Council, 2022a), while NTs delivered consultations online.

Notwithstanding practitioners' habituation to COVID-secure ways of working, these were not typical of pre- or post-pandemic ways of working, and therefore represent a limitation of the study's results: neither therapy was delivered in a manner necessarily representative of a future trial. Following the

official end of the pandemic in April 2022, acupuncturists relaxed the COVID-secure code, while nutritional therapists resumed some in-person working (although some have chosen to remain mainly online) (British Acupuncture Council, 2022; British Association for Nutrition and Lifestyle Medicine, 2023).

Recommendation: A future trial should not adopt COVID-secure ways of working unless there are compelling reasons to do so.

7.8 Discussion of general findings

This section deals with findings from the feasibility study that were not related to specific feasibility objectives or progression criteria, but may be of use to a future trial.

7.8.1 Protocol deviations

For discussion of practitioners' adherence to specified scope of practice, including the effect of intervention period duration, see **7.7.3**. For discussion and recommendations regarding scheduling of first appointments, see **7.7.3.v**.

7.8.2 Ethical approval

7.8.2.i Scope of NT practice

See **7.7.3.iii** for a discussion of scope of practice in relation to ethical approval.

7.8.2.ii Informed consent

The current, ongoing discussion exploring the applicability of research ethics to pragmatic trials (Nicholls et al., 2019; Goldstein et al., 2018; Taljaard et al., 2018; Kalkman et al., 2017; Platt, Kass and McGraw, 2014; Kass et al., 2013) suggests that current research ethics frameworks are based on a more explanatory trial model in that they assume trialled interventions offer greater risk and fewer benefits than routine practice; this therefore requires a stringent level of informed consent. But in a pragmatic trial, the inequivalence of risk/benefit between research and routine practice does not hold; where trial interventions decrement usual care risks, the traditional informed consent process may be either simplified or waived (Chan et al., 2021; Goldstein et al., 2018). This approach also helps preserve a degree of real-world verisimilitude despite trial participation (Irving et al., 2017; Kalkman et al., 2017; Konstantinou, 2012).

For Santé-AF, no simplification of consent was attempted. This was primarily on the grounds of safety: although acupuncture has an excellent safety profile that may be thought to compare favourably with the risks of usual care for AF, the safety profile of NT is unknown and it was anticipated that an ethics committee would therefore require a full process of informed consent; in the event, one focus of REC queries was indeed an extensive representation of the risks of both therapies to participants (**6.8.2**). No new safety evidence for NT is forthcoming, other than the very small amount provided by the Santé-AF feasibility study itself.

Recommendation: The same traditional consent process should be incorporated into a future trial to simplify the ethical approval process.

7.8.3 Identifying participants

Based on the PIC exit interviews (**6.8.4**), the process of identifying participants may be streamlined to make the study more attractive to PICs. The PIC search/screen process would benefit from the widening of eligibility criteria recommended earlier; both measures recommended in this section would shorten the identification process and reduce costs, as clinicians would not be required to spend a lengthy time screening.

Recommendation: The PIC search/screen log document should be redesigned to allow the search process to exclude more non-eligible participants before individual screening stage. Database codes should be provided for common GP databases to make the search process more efficient.

7.8.4 Qualitative data collection and analysis

Reflexive thematic analysis proved serviceable in the feasibility study to help mitigate the potential bias of a sole-researcher study and the effect of the researcher's professional qualification. While reflexivity is still desirable in a future trial to make researchers' positionality transparent, processes to support reflexivity may be more effectively practised within a team structure (Arias López, Andrä and Bliesemann de Guevara, 2023; Rankl, Johnson and Vindrola-Padros, 2021); this may allow other qualitative analytic methods to be deployed. This may consequently require a change in qualitative sampling methods, data collection methods, and approaches to issues such as data saturation and participant co-production. This decision should be taken in the light of associated decisions regarding whether to nest case reports in the trial (**4.1.3.iv**); it also has implications for the sampling process, as described below.

7.8.4.i Sampling for interview

The maximum variation sampling strategy used to sample n=16 interviewees was unsuccessful (**6.8.6**). While the insufficient variation required to fulfil all factors is not anticipated to be an issue in a future trial with a larger sample size, the factors themselves may require reconsideration, as others may be more closely related to a future trial's outcomes.

For instance, while duration of diagnosis is an important covariate for quantitative analysis, it may not be as influential in the qualitative data. An alternative factor that may stand in a more direct relationship to the trial's primary outcomes may be the participant's self-rated symptom severity and related HRQoL; this could be determined at pre-randomisation stage by asking participants to complete the symptom-related sections of the AFEQT questionnaire to guide allocation to interview. Additionally, omitting the factor of participants' group allocation (i.e., Acupuncture, NT, Usual Care) led to an unbalanced sample across the groups, which should be corrected in a future trial.

Dichotomisation of the factors may not be a helpful strategy to obtain a range of qualitative data from a representative sample of a future trial's population; however, it may introduce less bias in the qualitative data than the more traditional researcher judgement on participants' "ability to communicate experiences and opinions in an articulate, expressive, and reflective manner" (Palinkas et al., 2015, p.2).

Qualitative sampling is more often guided by precedent and the type of data analysis used (Gill, 2020); if a different qualitative analysis method is adopted in a future trial, this may influence sample size and sampling strategy. If saturation is used as a determinant of sample size, it should be noted that even with the duplication of some factor permutations in the feasibility study, saturation was not reached; new data was still emerging at the end of the interviews at both baseline and follow-up, and a future trial may wish to consider extending an interview sample size in view of this.

Recommendation: If a future trial retains the maximum variation sampling strategy, it should consider the recommendations above to increase breadth and richness of data derived from qualitative methods. However, a different method of qualitative data analysis may be used in a future trial, which may guide sampling strategy.

7.8.5 Benefits and harms of the interventions

7.8.5.i Benefits of the interventions

While a sample of n=25 at follow-up is not sufficient to robustly demonstrate benefit for either intervention, numerous examples of benefit were reported by participants in both intervention groups, including improvements in AF symptoms, improvements in other symptoms, improvements in feelings of general wellbeing, and improvements in self-efficacy (**6.4.2.iii**).

7.8.5.ii Harms of the interventions

While a feasibility study cannot reliably report evidence of harms associated with an intervention due to small sample sizes, it is good practice to report unintended consequences of an intervention (Abdel Shaheed et al., 2022; Eldridge et al., 2016b; Hodkinson et al., 2013). These are discussed below.

7.8.5.iii Safety

Santé-AF used unequal allocation (2:2:1 in favour of the active intervention groups) partly to maximise the power of the intervention groups to detect adverse events. Data on the safety of both interventions was collected during the study (**6.8.3**). While the study sample size is not sufficient to reliably report on the safety of either intervention, this study found no indications of a harms profile similar to that of conventional AF treatments for either intervention (**2.1.8.iii**).

The safety of acupuncture provided during Santé-AF is in accordance with the profile and extent of adverse reactions in other studies (Fei et al., 2019; Chan et al., 2017; Witt et al., 2009; MacPherson et al., 2001) in that adverse reactions were minor, infrequent and self-limiting. In White et al.'s study of group acupuncture for knee osteoarthritis (2016), pain, bruising and symptom exacerbation were reported for 17 of 342 (4.9%) treatments, compared with similar types of events for nine of 85 treatments (10.6%) in Santé-AF. In Foster et al.'s feasibility study of acupuncture for pregnancy-related back pain (2016) and a feasibility study of acupuncture for overactive bladder (Hargreaves, Harding and Clarkson, 2021), a small bleed at the needle site was regarded as an adverse reaction; by contrast, small bleeding events were not recorded by Santé-AF practitioners ("I wouldn't consider that an adverse reaction – a small bleed can be therapeutic" (P1/A)).

To the researcher's knowledge, the safety of nutritional therapy (NT) has not been studied. Although the safety of individual nutritional strategies has been investigated to some extent, the safety of an intervention that combines individual strategies does not appear to have been a topic of investigation, and accordingly there is no research against which to contextualise Santé-AF's findings.

One adverse reaction was observed in the NT group during the study (**6.8.3.ii**), although opinion was divided between the Trial Steering Committee, the participant and the participant's GP as to whether this was in fact an adverse reaction to NT or more an idiopathic reaction to medication coupled with unaccustomed exertion. The effects were, by the participant's own description, "inconvenient and detracted from my quality of life quite considerably" (4/142/NT) but were reversible and did not conform to the criteria for a Serious Adverse Event (National Institute for Health Research, 2016). By these criteria, there would seem to be no substantial evidence of harms

associated with the NT intervention (SPIRIT Electronic Protocol Tool & Resource (SEPTRE), 2020) and therefore no recommendation to remove NT from a future trial.

Recommendation: A future trial should continue to collect safety data on the two interventions in addition to the Usual Care group, to build the safety evidence-base for both therapies and to adhere to the ICHOM standardised outcome set.

7.8.5.iv Other harms of the interventions

Other possible harms associated with the interventions were observed throughout the study.

In the Acupuncture group, the geographical distribution of participants relative to the acupuncturists' premises involved lengthy travel times, and therefore costs, that were exacerbated by traffic at certain times of day (**6.4.2.iii**). Travel time was not recompensed, and although travel expenses were subsidised, it is likely that the expenses of participants living further away would not have been met by the standardised amount. This may have discouraged some patients from participating; in a future trial it may depress recruitment and/or retention.

The cost and effort of implementing dietary recommendations were mentioned by one participant as an unanticipated negative effect of the intervention (**6.8.3.iii**). Significantly, this comment was made by the only participant in the NT group responsible for implementing their own dietary changes (it was confirmed with NTs that all other participants had partners who implemented dietary changes). It can be speculated that (i) cost/effort of dietary change were neutral or negative for other participants; (ii) other participants were unaware of the cost/effort; or (iii) other participants simply did not comment; data on this issue was not actively collected and therefore the true impact of dietary change cost/effort remains unknown. It is possible that, had more Santé-AF participants been responsible for implementing their own dietary changes (and assuming cost/effort was positive rather than neutral or negative), greater numbers of NT participants may have withdrawn, demonstrated lower adherence, or reported lower ratings of intervention acceptability. See also the discussion of the effect of preferences in relation to the cost/effort of implementing NT (**7.1.2**).

It is within the scope of routine practice for NTs to handle the cost and effort of dietary changes in a sensitive manner adapted to the requirements of individual participants. Alternatively, a budget may be provided to offset the costs of dietary changes during the trial, although this raises the question of continuing provision at end-of-trial. There is also the ever-present spectre of decreased pragmatism: while it is unacceptable to place financial burden on participants in a study, the provision of cost subsidies inevitably reduces the generalisability between study treatment delivery and real-world delivery. A future trial may find it helpful to collect data from NT group participants on the costs and effort required to implement changes; these should be included in mixed-methods analyses of the effects of interventions.

Recommendation: A future trial should consider reimbursing full travel expenses.

Recommendations have been made elsewhere regarding location of practitioners in relation to PICs' catchment areas (**7.1.2.ii**). A future trial should emphasise to NTs the requirement to advise dietary changes appropriate to participants' time and financial resources, and should collect data on the costs and effort required to implement changes.

7.8.5.v Harms for practitioners

There were misunderstandings around the question of discontinuation of study participants on personal safety grounds for the Acupuncture practitioners (**6.8.8**). This not only represented an element of potential jeopardy for practitioners, but also a departure from routine practice.

Recommendation: The requirement to apply usual judgement to the question of personal safety should be strongly emphasised to practitioners in the training workshops for a future trial, to avoid future misunderstandings regarding self-determination of safety, jeopardy to practitioners, and any threats to the principles of pragmatism. To support this, the practitioners' study manuals should be amended to this effect.

7.8.6 Methodological findings

7.8.6.i Reflexivity and positionality

Positionality can be understood as aspects of personal and professional identity, including those related to political and religious beliefs and cultural norms; and those related to power and privilege, such as language, race/ethnicity, dis/ability, education, wealth, age and sexuality (Brown, 2022). Researchers' positionality shapes the interpretation of data and the eventual production of knowledge (Holmes, 2020; Savin-Baden and Major, 2013); in relation to qualitative research, an active awareness of positionality may be understood as an obligation that supports both the principles of research integrity and the internal validity, or trustworthiness, of the specific research project (Massoud, 2022; Wilson, Janes and Williams, 2022). For Santé-AF, some of the mechanisms to balance individual researchers' positionality, often via teamwork, were unavailable (Rankl, Johnson and Vindrola-Padros, 2021), and the study's sole-researcher status amplified the potential influence of researcher positionality on study design and methods.

To help maintain awareness of the potential effect of her positionality on the study, the researcher developed a positionality statement (see **Appendix A**, Miscellaneous section). In the statement, the researcher acknowledged additional aspects that had the potential to influence Santé-AF, including her professional qualification and status as a practising acupuncturist.

The positionality statement became a key element in reflexive research practice, defined as those practices in which "researchers self-consciously critique, appraise, and evaluate how their subjectivity and context influence the research processes" (Olmos-Vega et al., 2023, p.1). Fundamental to reflexive practice was a reflective research journal, kept from the inception of the project; this in turn helped to further develop the positionality statement itself. In the research journal, the researcher employed the Gibbs Reflective Cycle (Gibbs, 1988) to understand incidents and experiences that may have been shaped by her own positionality and/or unconscious bias (a regular habit of the researcher's acupuncture practice). This supported her to bring to conscious awareness the influences that arose from aspects of positionality, and to mitigate these where necessary. In particular, the evaluation stage of the cycle was used to consider whether the researcher's positionality had the potential to introduce research biases that would affect study results; where such biases were considered possible, the action plan stage of the cycle was used to attempt to minimise the effects of positionality in similar future circumstances.

Specific aspects of the researcher's positionality, their effect on the study, and their mitigations, have been discussed under the relevant sections in this chapter (**7.1.3.i**: Bias in practitioner recruitment; **7.11.1**: Confirmation and observer biases). This section will reflect on two additional aspects of positionality and reflexivity: the researcher's professional positionality in relation to participants and practitioners, and the role of the study's funder, and will aim to show the ways in which the researcher's use of reflexivity contributed to her learning.

The researcher's professional positionality

In relation to participants, the researcher's professional status as a qualified, practising acupuncturist gave rise to several incidents that were opportunities for reflection, supporting reflexive research practice and the active awareness of positionality.

Initially, reflexivity was used as a means of noting and mitigating bias. For example, the first of the extracts from the reflective research journal (**6.8.7**, Professional "lens") the researcher notes identifying in the participant a clear pattern of disharmony (in Western terms: emotional stress/frustration) and her informal suggestion that the participant should alleviate this by taking some exercise of a type they had previously found beneficial. The reflective cycle was used in the journal to *describe* the incident; to voice the researcher's conflicted *feelings* of self-censure regarding her lack of vigilance in responding as a practitioner and, complicating this, a degree of pleasure and pride in her professional capability; to *evaluate* the experience, noting that it clearly had the potential to affect the participant's study outcomes (a bias); to *analyse* the incident to understand its features, including how to recognise them in future; to *conclude* with a summary of

learning from the experience; and to make an *action plan* to recognise the features of this experience when they appeared in future, internally acknowledging the pleasure of making an accurate diagnosis but managing outward behaviour by "bracketing" the researcher's professional knowledge and skills (a technique similar to that used by phenomenological researchers (Thomas and Sohn, 2023)). The research journal records several similar incidents where the researcher's professional "lens" was activated by participants' disclosures, and the mitigation of potential bias as a result.

Other entries in the journal reflected on the researcher's relationship to the study's practitioners and how it was influenced by her professional positionality. Again, these were often focused on mitigating potential bias:

> Found [the NTs' peer supervision group] uncongenial. They were a bit niggly with each other and with me... I don't *think* I did anything to provoke that... [18th March 2022]

And by contrast:

> Did the acus' peer supervision group yesterday afternoon... they wanted to include me as an equal, but of course I declined. It didn't bother them... they [had] a joyful, no-holds-barred discussion... I followed in their wake, frantically scribbling extremely useful notes (for practice as well as S-AF!) [4th April 2022]

The reflective cycle, applied to this experience, suggested that the researcher's enjoyment of the acupuncturists' group may have materially influenced the quality of analysis for this data: "am I spending more time on the acus' queries, issues, etc, just because I get it?". Later entries in the journal, reflecting on the experience of analysing the data and writing up the thesis, underscored the possibility of unconscious bias, and consequent research bias, in this area:

> Just re-reading the latest version of the Methodology chapter... noticing that I've illustrated the "truly" complex intervention with acu examples, not NT, partly because they're Acu 101 and I know them well, and partly because there's so little research on NT process (or outcomes!), it's such a new discipline... But while all that is undeniably true, I can see the unconscious bias at work... it's just easier for me to talk about acu. I shouldn't just reach for the acu stuff because I know it, that's... lazy. [5th February 2022]

Application of the reflective cycle to this incident led to the researcher returning to the Methodology chapter and rewriting it to illustrate the concept of the "truly" complex intervention using examples from nutritional therapy as well as acupuncture.

While this bias-focused use of the reflective research journal was helpful, the journal also revealed the researcher's positionality as a positive resource capable of augmenting the depth and criticality of the study (Olmos-Vega et al., 2023). An example of this can be seen in the third excerpt from the

journal given in section **6.8.7** (Gender "lens"). Following this interview, prompted by her feminist positionality, the researcher retrospectively analysed her notes/recordings from informal chat around assessments or equipment collection/delivery, discovering that participants' partners, rather than the participant themselves, had borne the burden of dietary change. For instance, 2/481/NT alluded to his wife "really getting on board with [diet change]" and "eating earlier in the evening, a wider set of meals, more organic stuff, no red meat at all" (paraphrased) while 4/385/NT said his wife had changed the couple's shopping lists and now went to the shops every two days to buy fresh fruit and vegetables. This "interstitial" data (i.e., not present in the data collected by formal methods) suggested that male NT participants were often unaware of the cost/effort involved in dietary change and were therefore not reporting it in questionnaires and interviews; analysis prompted by the researcher's feminist positionality therefore brought to light a new perspective and an important issue for a future trial (discussed in section **7.8.5.iv**). Writing this incident into the journal and applying the reflective cycle, the researcher became aware that in this instance her positionality had helped to enhance the feasibility and real-world generalisability of a future trial.

Supporting researcher learning

Use of the reflective research journal supported the researcher's learning by producing a more nuanced understanding of "bias" as a concept in relation to positionality and reflexivity. Where the researcher had initially set out to use reflexivity simply as a means of neutralising bias in the trial, application of reflexive principles led to an understanding that in qualitative research no such neutrality is achievable, or even desirable (Olmos-Vega et al., 2023; Daniels, Gillon and Casson, 2021). Instead, qualitative researchers embrace and explore subjectivity and its influence on the processes of co-constructing meaning (Berger, 2015). A later entry in the reflective journal illustrates this understanding:

> [I] feel a bit odd saying this, but I'm really recognising the ways in which, when I started this PhD, I thought doing a trial was about *eliminating bias* and that really influenced my approach and the trial methods... I was constantly apologising for being an acu[puncturist]... Five years on, ... [that] seems so naïve... "bias" is a narrow definition, fundamentally a quantitative (countable) entity, whereas a qual[itative] researcher would acknowledge "bias" (subjectivity) as a quality – and more important, ineradicable... so the reflexive focus shifts to recognising it, making it explicit, mitigating it where needed, but basically seeing it as integral... even a positive!... I'd argue that now, but when I started I wouldn't have dared to stand up to [supervisor] in that way – I think [their] positivist views had a big influence on me at the start. But now I can see that's just [their] positionality! [12th September 2023]

Role of the funder

Investigation of funding sources (appropriate charities, academic sources and funding bodies, via internet research and consultation with academic supervisors and the researcher's wider networks) revealed no impartial source of funding for which the researcher and the research were both eligible. In the UK, the lack of funding for complementary medicine research can be seen as the result of interlocking structural factors hampering research into complementary therapies, and in particular the teaching of professional prequalification courses in independent educational institutions rather than universities (Veziari, Kumar and Leach, 2022; Veziari, Leach and Kumar, 2017). Since the UK's independent institutions place greater emphasis on the teaching of therapeutic skills than research skills (British Acupuncture Accreditation Board (BAAB), 2024), this situation fails to develop the therapies' research skills base; it also hinders access to research pathways and funding, since many research grant-making bodies will not fund research that is not supported by legal structures and governance frameworks most readily available via membership of a university (UK Research and Innovation (UKRI), 2023). For these reasons, independent research done by complementary medicine researchers is often of poor quality, creating academic mistrust which in turn perpetuates the absence of professional courses taught in universities; and so the vicious circle goes round (Charlesworth, 2022; Veziari, Leach and Kumar, 2017). Funding for research into complementary medicine is also not accessible via a commercial route, since there are few commercial interests at play (House of Lords Select Committee on Science and Technology, 2000). In summary, for the majority of UK-based researchers in complementary medicine there are vanishingly few funding opportunities; those that do exist are available from organisations that exist to promote complementary therapies, that may not be subject to appropriate governance frameworks or adherence to the principles of research integrity. This situation is arguably analogous to trials of medicinal products whose funding is derived from suppliers or manufacturers of the product under investigation, and to that extent it demonstrates clear potential for sponsorship bias (Jefferson, 2020; Lexchin, 2012).

For Santé-AF, initial funding of £10,000 was provided by the British Acupuncture Council (BAcC), the UK's leading professional membership and regulatory body for traditional acupuncturists, of which the researcher is a member. An equivalent funding application to the British Association of Nutrition and Lifestyle Medicine (BANT) was rejected on the grounds that membership fees were under pressure to meet objectives more directly related to member benefit (see **Appendix A**, Miscellaneous section). The initial funding for Santé-AF was therefore provided by the BAcC alone. The researcher requested a letter from the BAcC confirming that "provision of funding does not imply any influence exerted by BAcC over your independent decisions regarding study design, procedures, findings or eventual dissemination", which was duly provided (see **Appendix A**, Funding and costings section).

Despite this, issues of sponsorship bias arose during the project: verbal comments were made to the researcher by senior BAcC personnel regarding (i) a desire for the study to demonstrate the positive effects of acupuncture, and (ii) the use of BAcC funding to conduct a study investigating an additional therapy to acupuncture. The application process had been transparent: BAcC funding was granted in full awareness of the likely absence of equivalent BANT funding and the fact that, as a feasibility study, investigation of effectiveness was not part of the study's objectives. Although they were jocular in nature, the comments were in breach of good practice in research sponsorship governance (Health Research Authority, 2017), and generated some discomfort for the researcher.

Santé-AF's design and processes did not change as a result of these comments. However, to help mitigate the financial difficulties for BAcC members who were compelled to close their clinics during the pandemic, in March 2020 the researcher offered to forego the second half of the grant funding with a view to funding the remaining £5,000 personally. The BAcC declined this offer and the entirety of the grant was eventually delivered. The researcher reflected on this situation, concluding that the comments had materially influenced this decision.

Recommendation: Where research grants are provided by organisations representing the therapies under investigation, these organisations should undertake research integrity and governance training and practise these principles during their administration of research grants.

7.8.6.ii Nested case studies within a pragmatic RCT

In **Chapter 4**, the difficulties were discussed of using an essentially reductionist investigatory approach to represent the effects of individualised holistic therapies. An argument was made for the use of individual case studies or case series, nested within a pragmatic RCT, to augment the group-level findings produced by the RCT with a representation of change meaningful at an individual level.

Santé-AF was a feasibility study and could not investigate the effects of treatment at either individual or group level. Neither did it incorporate an objective to investigate a new extension to existing methodologies. However, it did demonstrate the feasibility of collecting individual-level data in both quantitative and qualitative forms. Individual semi-structured interviews were demonstrated to be feasible, and to produce rich, nuanced data capable of evidencing individual-level outcomes and enhancing qualitative understandings of clinically meaningful differences for a range of participants with AF.

In the feasibility study, this data was mainly not analysed as it was not relevant to feasibility outcomes; however, some indication can be gathered from **6.4.2.iii**. Here, participants discuss "whole person effects" (Paterson and Britten, 2003) such as changes in self-confidence, motivation and self-efficacy, and a range of contextual effects such as the costs and effort involved in

adherence, emotional negativity, changes in HRQoL associated with the interventions, changes in participants' sense of wellbeing, and logistical difficulties. This type of data may be incorporated within reports of trials as individual case studies, short "vignettes" (Keane et al., 2012) or co-published case series; individual-level qualitative data may illustrate or explicate the relationships within and between cases to give a better understanding of the effects relating to particular contexts, while study-level data may provide the wider contextual background indicating the causal evidence for the intervention at a group level.

The nesting of case studies/series within a pragmatic trial represents an area for future methodological development. Research may begin with a review of current literature to determine the extent of any existing use of this model, perhaps in other fields such as the social sciences or education, and to examine the possible applications and/or adaptations of this in healthcare. Methodological guidance is required, which may need to be adapted from other fields if applicable; reporting guidance may similarly need to be devised and/or adapted; and practical, informative methods are needed for synthesising individual-level analysis with group-level analysis to allow each to inform the other at all stages of design, implementation, analysis and reporting. These tasks may be the province of a working group of methodologically-focused experts aiming to achieve consensus on methodology together with a typology of approaches and methods.

Recommendation: A future trial may wish to incorporate a workstream for methodological development of the nested case-study model exploring the "extension" to the pragmatic randomised controlled trial methodology proposed in **4.1.3.iv**. The trial may also consider deploying this "extension" in its own design, aim and objectives. However, even if this methodological "extension" is not formally deployed within the trial, the use of qualitative data on participants' experience of AF and of the trial's interventions should still be incorporated into mixed-methods analyses to produce a more nuanced and representative indication of the interventions' effects.

7.8.6.iii Informing clinical practice

It is beyond the scope of this feasibility study to inform clinical practice, but a future trial may wish to use treatment-related data collected from practitioners – enhanced by case study material – to inform future clinical practice (Hutchinson et al., 2022). This study demonstrated the feasibility of collecting this data via log books and interviews with participants and practitioners.

Recommendation: A future trial should publish its findings regarding treatment strategies for AF in both therapies, including case study material, to inform clinical practice in acupuncture and NT.

7.9 Sample size calculation for a future trial

In their 2006 paper, Kraemer and colleagues warn against the use of pilot/feasibility effect sizes in calculating sample sizes for a future trial, arguing that "the two most likely outcomes are that (1) studies worth performing are aborted and (2) studies that are not aborted are underpowered" (p.484). These arguments have been endorsed by many statisticians since their publication (Freedland, 2020; Bell, Whitehead and Julious, 2018; Westlund and Stuart, 2017; Ukoumunne et al., 2015) and have been strengthened by additional rationales drawn from an increasingly patient-centric agenda urging the use of effect sizes meaningful to patients.

It is also likely that a sample size calculation based on the feasibility data would have imprecision resulting from the non-normal distribution induced by a small sample size (n=4) in the Usual Care group (Teresi et al., 2023). Treatment effects are also likely to have been overestimated in this feasibility study as a result of various biases including the effect of a single-centre study (Bafeta et al., 2012; Unverzagt, Prondzinsky and Peinemann, 2013).

It is also widely contended that unblinded trials, such as this feasibility study, carry a risk of overestimating treatment effects, particularly where subjective and/or self-reported outcome measures are used (Probst et al., 2016; Juni, Altman and Egger, 2001). However, the effect of blinding and subjective outcome measures on estimated treatment effect has been questioned in a recent analysis of 142 meta-analyses, which found no average difference in estimated treatment effect between trials with and without blinding of participants, healthcare providers and outcomes assessors; there was also no clear impact of subjective outcomes on treatment effect estimate (Moustgaard et al., 2020). Notwithstanding these findings, the debate continues regarding the overestimation of treatment effects associated with patient-reported outcome measures. The most frequently recommended mitigation is the use of a combination of subjective and objective measures (Kluzek, Dean and Wartolowska, 2022; European Medicines Agency, 2014). Santé-AF demonstrated the feasibility of using such a combination, although for this to be effective in mitigating the overestimation of treatment effects, a composite end-point comprising the four main outcome measures (EQ-5D, AFEQT, symptom diary and CardioSTAT® monitor) would have to be specified – which was not the case in this feasibility study. There is, therefore, a risk of inflated treatment effects arising from this study.

For all these reasons, while a sample size for a future trial was calculated in the feasibility study (**6.9**), point estimates of effect from the study did not guide this calculation, and the calculation remains illustrative rather than definitive.

7.9.1 Statistical methods versus Minimum Clinically Important Difference

If pilot/feasibility data is inadmissible as the basis for calculating a future trial's sample size, other methods are no less debated. The use of traditional methods such as literature review and the adoption of precedent may not produce reliable results unless the PICO of a future trial is sufficiently similar to the precedent (which may be unattractive to funders, thereby depressing overall future trial feasibility) (Freedland, 2020). On the other hand, the use of purely statistical methods for sample size estimation may be thought to omit an element of patient input required by an increasingly patient-centric agenda in research, and risks exposing patients to the safety issues and burdens of trials that are either under- or over-powered to detect effect sizes that would make a meaningful difference to them (March et al., 2010; MacPherson, 2004).

In their 2006 paper, Kraemer et al. instigated a concept they called the "threshold of clinical significance" (p.487): the smallest effect that would reduce clinicians' uncertainty about the interventions being investigated. The threshold of clinical significance functions as the context against which to judge feasibility and justifiability of a future trial:

> How many patients should the ethical clinician be willing to treat with *T* to achieve 1 success more than would have been achieved with *C* ?… If failure meant death, the answer might be different than if failure meant a smaller reduction in symptoms… How to evaluate clinical significance… is a question that statisticians cannot and should not answer. It is a question on which clinicians, consumers, and clinical researchers should attempt to reach consensus" (p.488)

Use of purely statistical methods simply powers a future trial to detect a given *size* of effect (assuming such an effect exists). Even setting aside the caveats in this section regarding the accuracy of effect size generated by this feasibility study, the question remains as to whether a given effect size is *qualitatively* significant – especially for measures important to patients, such as HRQoL. The concept of what could be termed a qualitatively significant effect size has been given various names, including the *minimum clinically important difference* (MCID) as defined by McGlothlin and Lewis (2014): "the smallest benefit of value to patients… a patient-centred concept, capturing both the magnitude of the improvement and also the value patients place on the change" (p.1342); or the *minimum important difference* (MID) (Sim, 2019), defined as a concept informed by clinical judgement and patient perspectives.

Santé-AF's primary outcome measure was the self-reported Atrial Fibrillation Effect on QualiTy of life (AFEQT). Various values have been calculated for a minimum change in AFEQT score; for instance, Dorian et al. (2013) suggest that a change of 18.9 ± 20.7 points in AFEQT score corresponds to a moderate improvement in global HRQoL using anchor-based methods, and this value was adopted as an MCID by a study that considered HRQoL in relation to catheter ablation (Azizi et al., 2019). In another study, investigators used the US-based ORBIT-AF registry study to calculate a clinically

important difference (CID) within-participants after a 12-month period of conventional treatment. The authors used two statistical methods to arrive at a change score of 5.4 points (95%CI = 3.6–7.2), suggesting that AFEQT score changes as small as ≈5 points may be clinically relevant (Holmes et al., 2019). However, the authors concluded that calculating a "universal" CID using statistical methods may not reflect patients' concerns, and that such concerns should be included in a future trial's sample size calculations. This CID was used in calculating the "illustrative" sample size for a future trial in this thesis (**6.9**).

To use an MCID in calculating trial sample size is implicitly to balance statistical considerations with qualitative considerations, specifically the qualitative considerations of the patient (in other words, "statistical significance is necessary but not sufficient" (Freedland, 2020, p.853)). A future trial of Santé-AF is likely to need multifactorial input to inform a sample size calculation, and the patient's perspective may be considered useful alongside the perspectives of clinicians, researchers and statisticians. In this feasibility study, the patient and public involvement (PPI) panel advised on the nature, but not the thresholds, of outcomes that were of importance to people with AF (**5.3.1.ii**); this role should be expanded in a future trial.

7.9.2 Unequal allocation ratio

Another factor that may be important when calculating a sample size for a future trial is the unequal allocation ratio used by Santé-AF. It has been argued that a 2:1 ratio necessitates an increase in required sample size of approximately 12% (Hey and Kimmelman, 2014; Meinert, 2012; Vozdolska et al., 2009), although this is disputed by a number of authors who argue that power is only compromised when ratios approach 3:1 (Gupta et al., 2021c; Chandereng, Wei and Chappell, 2020; Torgerson and Torgerson, 2008; Dumville et al., 2006). The unequal allocation ratio was chosen for greater power to detect differences between the two treatments compared with each other (thereby strengthening a future trial's ability to inform clinical practice), and to report any safety issues particularly for nutritional therapy; for these reasons, the allocation ratio may be considered important to preserve in a future trial. A future trial should therefore consider whether the unequal allocation ratio requires an increase in sample size.

7.9.3 The effects of pragmatism and complex interventions

It is also recommended that a future trial should consider the possible effect on sample size of pragmatic trial design for two complex interventions. As Patsopoulos observes, "pragmatic trials are a race towards maximal heterogeneity in all aspects" (2011, p.218). A larger sample size may be required to reliably indicate the effect of the interventions, given the variability in parameters such as treatment response and the standard care received by all participants (particularly given

pragmatically wide eligibility criteria likely to enfranchise a heterogenous cohort); within-participant variability in the CardioSTAT® data, as observed in the feasibility study (**Table 33**); and variation in adherence and flexibility in intervention delivery (Giraudeau et al., 2022; Skivington et al., 2021b; Rengerink et al., 2017; Welsing et al., 2017).

7.9.4 Cluster effects

Cluster effects may arise in individually randomised trials in which multiple participants are allocated to practitioners delivering the intervention (Wilson et al., 2016; Lee and Thompson, 2005) because the practitioners' skills and other non-specific effects may be directly related to their participants' outcomes; this introduces a source of bias by reducing variation in outcome between participants treated by the same practitioner, and violates many statistical tests' assumptions of observation independence. In this way, clustering reduces the effective sample size and consequently reduces the trial's power to detect an intervention effect (Oltean and Gagnier, 2015; MacPherson, 2004); calculating a future trial's sample size using data that has not accounted for clustering may lead to incorrect sample size calculations, confidence intervals and statistical significance levels for treatment effects (Chuang, Hripcsak and Heitjan, 2002).

It is reasonable also to hypothesise that the effects of clustering in reducing power may be compounded if the intervention itself is complex and comprises multiple permutations of specific and non-specific effects. In addition, the more experienced the practitioner, the better the patient outcomes are likely to be (Conroy et al., 2020; Biau et al., 2008).

The standard approach to analysis – i.e., using fixed effects models – would effectively restrict the results to the trial's practitioners rather than allowing generalisation to the wider population from which the practitioners had been sampled; in pragmatic trials, random effects models are recommended to mitigate cluster effects instead (Conroy et al., 2020). Lee and Thompson (2005) suggest that the potential for cluster effects should be anticipated at design stage, and sample size should be increased to avoid the loss of power that clustering confers.

7.9.5 Approach to sample size calculation

Bearing in mind these qualifying factors, sample size calculation may be a complex exercise, requiring consensus; guidance on how to mitigate some qualifying factors is sparse and the exercise may result in some best-guesswork. If all qualifying factors discussed in this section are taken into account, it is possible that the final *ideal* sample size will be infeasibly large. It may be considered advisable for a future recalculation exercise to take pragmatic decisions so that a future trial's sample size remains feasible, while achieving a considered, workable balance between key parameters such as patient-relevant outcomes including meaningful effect size, sample size and

power, and consequent generalisability of results to wider real-world contexts. Because a reliable reduction in uncertainty with regard to sample size is beyond the remit of this study, this aspect of feasibility therefore represents arguably the largest area of uncertainty remaining unaddressed by this feasibility study.

Recommendation: A future trial should incorporate a limited feasibility exploration into its early stages, in which a PPI panel, together with clinicians, researchers and statisticians, attempt to achieve consensus on a workable set of trial parameters, taking into account those qualifying factors described above which are deemed relevant. Using this workable set of trial parameters, a sample size should be recalculated.

7.10 Limitations of this feasibility study

Santé-AF was subject to various limitations. In terms of feasibility, these are mostly identified in relation to individual objectives and discussed in context elsewhere in this chapter. Additional limitations are discussed here.

7.10.1 Single-centre study

This was a single-centre feasibility study and as such, has limited generalisability in terms of feasibility (Bafeta et al., 2012); additionally, some biases specific to the single centre are discussed in **7.1.3.i**. Some parameters of a future trial, including practitioner availability (Coates et al., 2020) and participant recruitment (Treweek et al., 2013), may require cautious interpretation when applied to multiple alternative sites/local areas.

Some limitations arose from the fact that all acupuncturists practised from a single clinic in central York (Worsley et al., 2017). This did not allow exploration of the benefits and disadvantages of multi-site locations of practitioners, although it did allow exploration of possible issues of contamination between practitioners (**6.7.5**).

7.10.2 Sex, ethnicity and minority representation

Santé-AF's participant group was ethnically imbalanced (100% white) (**Table 21**) (with the term "ethnicity" understood to encompass race (Cabinet Office, 2021)). The population in the local area where Santé-AF was conducted is 92.8% white (Office for National Statistics, 2022), but a more representative sample would have included n=2 or n=3 (6.7%–10.0%) non-white participants. Recruitment materials were available only in written English, while two of the four PICs were situated in rural locations with less ethnically diverse populations (Department for Environment, Food and

Rural Affairs, 2024). Both factors may have contributed to the failure to recruit a greater proportion of non-white participants.

Trials' inclusion of an ethnically diverse range of participants is important for several reasons, including generalisability and the ability to study effects of interventions for different ethnic groups (National Institute for Health and Care Research, 2022; NHS Health Research Authority, 2024). In particular, there are good reasons to include a representative range of ethnicities within atrial fibrillation trials, due to under-representation in existing trials (Norby et al., 2021; Tamirisa et al., 2021), and different management of the condition across ethnic groups (Eberly et al., 2021; Volgman et al., 2019) (see also **2.1.5.i**). A future trial conducted in the UK should therefore seek to include a more ethnically representative sample of the general UK population, using culturally competent trial designs and methods developed in collaboration with ethnic minorities to minimise ethnically-related barriers to recruitment (NHS England, 2023).

Another area of under-representation in Santé-AF was sex: only n=7 or 24.1% of the sample group was female. This finding is at odds with the female-dominant uptake of complementary therapies in the UK (Sharp et al., 2018; Hunt et al., 2010), but aligns with the wider picture of women's participation in cardiovascular trials, which is generally lower than the participation of men (Cho et al., 2021). Reasons for non-participation in Santé-AF include only one potentially sex-specific reason, that of caring responsibilities precluding attendance in person (**6.1.2**); however, it could be speculated that the trial's age range (≥45≤70) included a high proportion of women with caring responsibilities that may have disinclined them to take part (Matthews et al., 2024). Female participants' informal disclosures during assessments revealed that five of the total seven had at least one caring responsibility, including pre-school-age grandchildren with a full-time working single parent, living with the participant; a parent with advanced dementia living with the participant; post-school care for grandchildren every weekday; and providing domestic care for a nearby adult child with a learning disability. While this did not prevent participation, it was noted that one participant could not attend acupuncture appointments and another could not complete the follow-up assessment, both due to caring responsibilities. Recommendations for a future trial made elsewhere in this chapter may support greater inclusivity of women, including more local acupuncture clinics and a choice of online or in-person attendance for nutritional therapy.

The study did not collect data on participants' first language, disability status, protected characteristics or specific learning differences that may have presented barriers to participation, and therefore no conclusions can be drawn on this score. However, good practice indicates that recruitment materials and trial design should take account of an appropriate range of equality and diversity dimensions to remove as many barriers to participation as possible in a future trial (NHS

England, 2023). This would support more representative participation and thereby maximise the generalisability of results.

7.10.3 Limitations associated with sole researcher

Santé-AF was a doctoral research project, and as such, was the work of a sole researcher. This was associated with several limitations.

7.10.3.i Researcher positionality

The sole researcher's positionality may have influenced the feasibility study's results (Error! Reference source not found.). This was an unavoidable limitation of the study, and should be considered in relation to any interpretation and generalisation of its results to a future large-scale trial.

7.10.3.ii Blinding in a future trial

Blinding to intervention allocation mitigates the possibility that some trial personnel, including participants, practitioners, data collectors and analysts, may exercise conscious or unconscious personal bias while investigating a given intervention. A substantial limitation arising from the sole-researcher status of this feasibility study was the inability to blind most outcomes assessment: the researcher carried out randomisation and was therefore aware of group allocation while collecting and analysing data. While the study's outcomes were mostly feasibility-related rather than effect related, it remains impossible to mitigate entirely the risk of bias arising from the work of a sole researcher (who is also a trained and practising professional in one of the interventions investigated by the study) through all domains of the study, including data collection, outcomes assessment and data analysis.

Participants and practitioners in pragmatic trials of interventions are, in general, not blinded, as the aim is to investigate intervention effectiveness in real-world contexts; the practical effects of blinding may compromise generalisability in pragmatic trials' results (Dal-Ré, Janiaud and Ioannidis, 2018; Welsing et al., 2017). Santé-AF is an example of a study in which patient/practitioner blinding would compromise real-world fidelity of both therapies: while the needling component of acupuncture may be blinded for participants and practitioners to some extent (MacPherson et al., 2014), no other component of treatment may be blinded; and nutritional therapy by its nature cannot be blinded for either participant or practitioner. Blinding of participants and practitioners may therefore be considered contraindicated in a future trial of Santé-AF on grounds of both methodology and methods.

It is desirable to blind outcomes assessors to avoid bias in effect estimates (van der Ende et al., 2023; Hrobjartsson et al., 2012; Power and Hopayian, 2011; Noseworthy et al., 1994). However, this is related to the type of outcome being assessed: in general, existing research in this area focuses on clinician-applied assessments requiring some subjective judgement, which may be considered at greater risk of bias than objective measurements. Christian et al. (2020) and Zhang et al. (2022) suggest that the importance of assessor blinding in pragmatic trials varies with the outcome investigated, with subjective outcomes offering particularly high risk of bias. The majority of outcomes in Santé-AF were self-reported by participants; in this case, the assessors were effectively the participants themselves and to the extent that the participant role was unblinded, the assessor role was likewise unblinded, adding to the potential for bias especially in the light of participant preferences (**7.1.2**) or obsequiousness bias. It is also not possible to reliably blind a future trial's researchers assessing or analysing qualitatively-determined outcomes where those outcomes are related to intervention effect, as participants must necessarily discuss the intervention received in this context, thereby unblinding assessors and data analysts.

In Santé-AF, the only blinded assessors were Icentia's electrophysiologists (EPs) who analysed the CardioSTAT® data; EPs were blinded to group allocation as part of routine organisational procedures to maintain confidentiality of all patients wearing the monitor. This outcome's assessment, at least, can be robustly blinded in a future trial.

It must be concluded that it is not practical to maintain blinding of outcomes assessors for the majority of Santé-AF's outcomes, and this must represent an ongoing limitation of a future trial. Additionally, if earlier recommendations are adopted regarding practitioner data collection in a future trial (**7.5.3.ii**), this increases the possibility of risk of assessor-related bias.

7.10.3.iii Timescales

The limitations imposed by the sole researcher regarding timely scheduling of assessments at the start of interventions (**6.5.2.iii**) are not anticipated to be a problem for a future trial which has a team of researchers, and which is not conducted under the restrictions imposed by the COVID-19 pandemic.

7.10.3.iv Systematic review

The systematic review positioned at the outset of this study was limited by the fact of a sole researcher. This may have introduced biases in study selection, and in data extraction.

7.10.4 Limitations introduced by COVID-19

The feasibility study took place under the conditions of the COVID-19 pandemic, and some results may therefore have limited applicability in non-pandemic conditions:

- Known and unknown effects on willingness to participate (**6.1.2.i**);
- Effects on participant eligibility (**6.2.1**);
- Known and unknown effects on participant retention (**6.3.4**);
- Effects on intervention acceptability (**6.4.2.iii**);
- Effects on assessment acceptability (**6.5.2.ii**);
- Effects on the utility of the CardioSTAT® monitor (**6.6.1** and **6.6.4**);
- Effects on the overall acceptability of study participation (**6.7.1.i**), including intervention fidelity (**6.7.5**);
- COVID-19 also delayed the study start, which limited the possible length of follow-up (**5.3.1.i**).

Unless a future trial takes place under similar pandemic conditions, these limitations will not apply.

It should be noted that the COVID-19 pandemic was a dynamic phenomenon; its effects are likely to have been mitigated by the timing of the study in relation to pandemic progress (**Figure 6**). Recruitment began with PICs' Expressions of Interest in August 2021 and study participants were recruited from September 2021, some 18 months after the start of the first UK lockdown; the final follow-up assessment was conducted in May 2022, around 26 months after the start of the first lockdown. It may be speculated that feasibility objectives would have been more severely impacted, particularly those relating to participant, practitioner and PIC willingness to participate, participants' retention, and acceptability of intervention, assessment and overall participation, if the study had taken place earlier in the pandemic.

7.10.5 Limitations introduced by study funds

The study was funded by the British Acupuncture Council, with a total fund of £10,000. Restrictions in funding introduced several study limitations:

- It was not possible to provide a budget for supplementation, which restricted the scope of practice for NTs (**6.7.5**);
- It was not possible to provide CardioSTAT® ECG monitors for more than a third of participants; this gave a limited pool of participants to investigate the utility of the CardioSTAT® monitor and findings for this objective must therefore be interpreted with caution due to a small sample size (**6.6.4**);

- Translators could not be provided for the study. This is unlikely to have had a material effect on recruitment, since the local population comprised 94.9% speakers of English as the main language (**5.6.1**).

7.10.6 Limitations associated with the study of nutritional therapy

Nutritional therapy (NT) is a relatively new discipline, and this feasibility study is the first known randomised controlled trial to investigate its effects; as noted in **Chapter 3**, there is some evidence for specific nutritional interventions but no evidence for NT as a holistic therapy that combines specific nutritional interventions with a range of non-specific effects in an individualised per-patient context. The novelty of the therapy has imposed several limitations on this study, including the absence of an existing evidence base against which to contextualise results; the fluidity of professional parameters including practitioner qualification and training; typical treatment parameters; and the definition of the therapy itself. Partly as a result of this, Santé-AF used a more restrictive set of parameters to define NT than may accurately represent the therapy as practised in a real-world context. It has been recommended in this section that these parameters are investigated in order to define the therapy more closely, and with more real-world applicability, for a future trial.

7.10.7 Limitations associated with changes in hypothesised AF pathophysiology

As discussed in an earlier chapter, recent clinical thinking has begun to hypothesise a different mechanism of action than that traditionally assumed in the pathophysiology of AF, and therefore the extent of its causal link with frequently-observed comorbidities including stroke (**2.1.4.i**).

This was not a limitation for this feasibility study, but the change in clinical thinking is significant and may have implications for a future trial. If it can be rendered less speculative by investigation, current clinical thinking may to some extent position atrial myopathy as a stronger indicator/risk factor for AF sequelae, than AF itself (Gupta, 2021). While it is not possible to predict the effect of this on AF research, it may be speculated that if AF is thus decoupled from comorbidities, particularly those carrying high mortality risk, the focus of future therapeutic investigation may likewise move away from attenuating actual AF towards attenuating perceived symptoms, and also to improving HRQoL in the context of AF. This shift in direction is already evident (Seligman et al., 2020), but may be given impetus by further research into atrial myopathy. A future trial may therefore choose to take account of this in terms of its research questions, eligibility criteria and choice of primary and secondary outcome measures.

7.11 Biases of this feasibility study

Risks of systemic bias were considered, and attempts made to mitigate them during the design of this feasibility study; a consideration of their effects is incorporated contextually in the discussion above. Other applicable biases are discussed below.

7.11.1 Confirmation and observer biases

As the work of a sole researcher, the risk of confirmation bias could be thought endemic to this feasibility study, particularly as the researcher is also a qualified acupuncturist (i.e., despite not having delivered any treatment in the study, nonetheless arguably subject to a form of observer bias commonly associated with researcher/practitioner status (Daniels, Gillen and Casson, 2021; Yu, 2011)). This is closely linked to the bias that may arise from industry sponsorship, as the initial funding for Santé-AF was provided by the British Acupuncture Council; and additionally to reporting bias, in terms of the selection of analyses to report. These biases were mitigated in the following ways:

- **Conducting the study analyses** may be thought particularly prone to bias, particularly some qualitative analyses where interpretation may have been influenced by the researcher's professional and personal positionality. This was mitigated by the use of reflexive thematic analysis as an analytic method, and an ongoing reflective analytic memo journal that allowed the researcher to reflexively note and mitigate the influence of positionality on analyses (Braun and Clarke, 2021, 2019) (**6.8.7**). Some issues of interpretation were confidentially discussed with practitioners to compare interpretations of meaning (including practitioners in the alternative group in which the participants in question were not treated), providing useful triangulation for the sole-researcher perspective and therefore increasing trustworthiness and reliability of the qualitative findings. While it is not anticipated that the analysis of a future trial will be the responsibility of a sole researcher, this co-interpretive exercise would be recommended for a future trial if researcher roles were undertaken by practitioners.
- **Reporting the study results.** Care was taken to conduct and report all analyses as set out in the study protocol (**Appendix A**, Protocol and ethics section), except where these were not viable (e.g. **6.6.1**). Where analyses were found to be irrelevant to a future trial, they are not reported here but results have been made available in **Appendix D**.
- **Contextualising study results against the extant literature.** This was mitigated by careful searching and reporting of literature with a range of conclusions both consonant and dissonant with Santé-AF's findings. It should be noted that the range of published feasibility studies and pilot trials of complementary medicine is currently limited, and none

to the researcher's knowledge follow the specific PICOS of Santé-AF, meaning that contextualisation is limited and arguably of reduced value.

- **Dissemination.** Results are planned to be disseminated in a range of publications and by presenting at a range of conferences and events, including those specific to AF, specific to each therapy, and specific to complementary medicine as a whole.

7.11.2 Behavioural biases

7.11.2.i Hawthorne effects

For Santé-AF participants, the awareness of being studied may have led to misrepresentations of various true statuses, particularly as most of Santé-AF's outcomes were self-reported. For instance, when asked to keep a diet diary, participants tend to record more favourable versions of their actual diet; also, the act of keeping a diet diary may lead to real-world adjustment of quantity, type and quality of foods actually consumed (Tanweer et al., 2022; Li et al., 2021; Fowler et al., 2018; Turner-McGrievy et al., 2017).

Additionally, the fact that participants took their own anthropometric measurements (the results of which were unverifiable by the researcher due to online working during the COVID-19 pandemic) may also have allowed the opportunity for Hawthorne effects. Anthropometric measurements may be regarded as somewhat objective when carried out by a trained professional (Casadei and Kiel, 2023); assuming that a future trial's measurements are taken by practitioners, participant-side Hawthorne effects may be reduced. Balancing this, practitioner measurement introduces the possibility of assessor bias, which may be mitigated by including the practitioner as covariate in analyses to correct for any biases in measurement.

Mitigating the Hawthorne effect is usually advised in terms of hidden observation or collection of data from registries (the latter also having the benefit of increasing the pragmatism of follow-up) (Konstantinou, 2012); unfortunately, neither mitigation is practical for Santé-AF, for reasons discussed elsewhere (**7.5.3.ii**).

Practitioners, as a type of participant in this feasibility study, were also potentially at risk of Hawthorne effects. This was observed in the study: practitioners' awareness of delivering treatments for a study contributed to modified practitioner behaviours that affected intervention delivery (and therefore, if replicated in a future trial, some aspects of generalisability to wider real-world contexts) (**6.7.5**). Practitioner training workshops – together with the recruitment process, the supply of regulatory documents, the legal documents contracting practitioners to the study, the study manuals, and the log books – may all have contributed to an awareness of being studied, and therefore increased the likelihood of Hawthorne effects for practitioners (in addition to reducing

pragmatism by potentially distorting routine practice (Worsley et al., 2017)). However, all documents and processes were necessary to maintain participant safety and research/data integrity, and to ensure practitioners were fully aware of the scope of practice in the study.

Recommendation: As participant-level Hawthorne effects cannot be entirely mitigated by design, a future trial should acknowledge the remaining bias as a limitation. Practitioner training workshops should emphasise an understanding of pragmatic trials as reflecting real-world practice, and therefore the need to maintain all aspects of routine practice (except those specifically modified by the trial). A future trial should explore this issue with practitioners, investigate any behavioural biases, and report these alongside the trial results, acknowledging them as a limitation of a future trial.

7.11.2.ii Apprehension bias

Apprehension bias (arguably a form of behavioural bias) was observed in Santé-AF in the specific form of blood pressure measurements that were higher than expected for three participants, and may have been higher or lower than their true value in a further three participants, due in all cases to a declared aversion to taking blood pressure readings (**6.5.2.ii** and **Table 31**). In a future trial, this may be mitigated by either requiring study practitioners to take blood pressure readings (**7.5.3.ii above**) (although this would not mitigate so-called white-coat hypertension (Ogedegbe et al., 2008)); or by allowing participants to take their own blood pressure readings at home over time, although this last must be balanced against the potential for measurement error when using uncalibrated equipment (Innes et al., 2021). Both methods may be employed if needed; if a proportion of measurements was taken by practitioners, this would reduce the number of participants taking their own blood pressure and therefore reduce the effect of measurement error from uncalibrated equipment.

8 Conclusion

This study has investigated the feasibility of a future large-scale trial investigating the effectiveness of two complementary therapies for atrial fibrillation (AF). Its feasibility objectives considered willingness to take part; eligibility criteria; participant retention; acceptability of intervention and assessment; the utility of the CardioSTAT® ECG monitor in a trial context; and the overall experience of study participation. Several additional parameters were also investigated, including intervention fidelity in trial conditions; the feasibility and effects of ethics approval processes; and the effect of the COVID-19 pandemic on feasibility. This chapter draws together a brief summary of the main findings and recommendations for a future trial; it also considers the strengths and limitations of this study; makes recommendations for future research; and concludes with a statement answering the study's research question.

8.1.1 Summary of findings and recommendations for a future trial

In relation to **willingness to take part**, this study found that despite COVID-19 pandemic conditions, AF patients were willing to participate in sufficient numbers to meet the required sample size, meeting the progression threshold. As participants' preferences for and against both interventions were discovered during the study, discussion of this objective suggested that a future trial may wish to take account of preferences to increase feasibility and generalisability, and mitigate biases; several designs were critically discussed in relation to this PICO. It was recognised the adoption of a preference trial design would introduce significant further uncertainty with regard to the feasibility of a future trial, and would likely require a further feasibility study if adopted.

PICs' and practitioners' willingness to take part was also investigated, and the study revealed several aspects of participation that could be improved to make the trial more attractive to both, thereby increasing feasibility. Several potential biases were detected in the feasibility study's recruitment of practitioners in the trial location, and recommendations were made to mitigate these in a future multi-centre trial.

The **appropriateness of eligibility criteria** was investigated by this study. As specified for the feasibility study, the criteria did not achieve the ≥60% progression threshold of eligible to identified participants. Critically considered, the eligibility criteria were found to be more explanatory than pragmatic, decreasing the generalisability of a future trial's results to a real-world context; they also lent complexity that resulted in some operational errors, added to participant burden, and potentially depressed recruitment. Three participants were randomised in error, and one participant was randomised in violation of the criteria; if replicated in a future trial, this would have decreased the reliability of the results. To increase feasibility and mitigate all these factors, it was

recommended that a future trial's eligibility criteria should be widened, particularly those concerning age, type and characteristics of AF.

Practitioner eligibility was also critically discussed with regard to pragmatism and feasibility in a future trial, resulting in a recommendation to retain the feasibility study's practitioner eligibility criteria.

Participant retention was investigated by the study, and was found to meet the progression threshold of ≥80% retention at follow-up. The feasibility study identified several aspects of its design that may be changed to increase retention in a future trial, including NTs' online/in-person appointments, and the location of practitioners' premises. Adjustment to these parameters may also increase recruitment and adherence (in terms of appointment attendance), and mitigate against differential loss to follow-up in groups. The issue of follow-up was also discussed with regard to the short follow-up period used by Santé-AF, especially for interventions that have been demonstrated to show longitudinal effects; a recommendation was made to add a longer follow-up to a future trial while acknowledging that there is significant uncertainty regarding the feasibility of this recommendation since it was not a parameter investigated by the feasibility study.

With regard to **intervention acceptability**, this study found that participants were, in general, satisfied with their group allocations, and found the two interventions highly acceptable. Both progression thresholds were met, but the feasibility study made several findings that could be implemented by a future trial to increase feasibility and generalisability of its results to a real-world context. These include consideration of a nested sub-study to examine treatment expectation in relation to outcomes for these therapies by AF patients; and a recommendation to monitor self-care/lifestyle advice adherence (targeting modifiable risk factors) more closely in a future trial, to understand its possible effect on outcomes.

The **acceptability of study assessments** was also investigated by the feasibility study; both progression thresholds may be considered to have been met, but the study revealed several aspects of the current design that could be modified to reduce participant burden in assessments, and to improve data integrity. Recommendations were made to increase data integrity by abandoning online working for a future trial's assessments; and to reduce participant burden by shortening and simplifying the questionnaires and interviews (some of which would happen naturally by the absence of feasibility-related questions and COVID-19-related questions). Further, if earlier recommendations regarding simplification of eligibility criteria are accepted, this would also mitigate participant burden with regard to eligibility checking (a form of assessment). To increase the pragmatism of study assessments, a recommendation was made for practitioners to collect some types of data at first and final appointments, although this must be balanced by the consequent effect on other parameters including a requirement for NTs to work in person, recompense for the

time taken to train practitioners in data collection methods and to collect data during appointments, and the possible depressive effect on practitioner recruitment.

Neither of the two progression thresholds relating to the **CardioSTAT® ECG monitor's utility** was applied. The first of these (agreement between the monitor and the symptom diary) was not possible to conduct, due to limitations in the CardioSTAT® data; however, it was clear from visual inspection of data produced by each method that there was very little correspondence between the two. This suggested that perceived symptoms were not necessarily indicative of active AF, leading to a recommendation that a future trial should retain both measures – the symptom diary as a measure of perceived symptoms, and the CardioSTAT® as a measure of active AF – as a combined subjective/objective measure which may also increase recruitment due to the removal of the eligibility criterion requiring participants to be "aware of their AF". To the extent that this reflects the AF population more closely, this would also increase real-world generalisability. The second progression threshold, the monitor's influence on participation and retention, was accepted as inappropriate and not applied as a progression threshold. Findings of the analysis were nonetheless useful for a future trial, suggesting that neither retention nor removal of the monitor would significantly affect participation or retention.

Investigation of the **overall experience of study participation** indicated that 96% of participants found study participation acceptable, exceeding the progression threshold of 75%; additionally the COVID-19 pandemic appeared not to have caused participants excessive worry with regard to study participation. Recommendations were made for modifications to increase acceptability, including reducing burden in study documentation. Practitioners' experience of study participation was also investigated: several recommendations were made to increase acceptability for practitioners, including changes to log books, communications, peer supervision opportunities and fee payments. Investigation of this objective also revealed several issues relating to the fidelity of interventions to real-world practice, including referral of participants, adjustments to the overall window of intervention delivery and delays in first appointment scheduling. If the effect of self-care/lifestyle advice is to be followed up in a future trial, a recommendation was made regarding practitioner adherence to the practice of giving self-care/lifestyle advice; and a further recommendation was made to consider lifting the prohibition on NT practitioners advising on supplementation, although this decision should be taken in balance with budget and ethics feasibility concerns. The COVID-19 pandemic represented a substantial change in delivery for both interventions, and this may be regarded as a limitation of the feasibility study since some aspects of intervention delivery cannot be generalised to a post-pandemic future trial.

A range of **general findings** led to recommendations and suggestions for a future trial, including allowance of an extended time period and preparedness for limitations in pragmatism associated

with ethical approval; changes to the participant identification process and documentation; the collection of a more complete and/or accurate dataset regarding effect modifiers such as duration of AF and comorbidities; and reconsideration of qualitative data analysis methods, including the process of sampling for interview. It was observed that, within the framework of a standard pragmatic RCT, the feasibility study had demonstrated the feasibility of collecting data of sufficient extent and depth to produce an application of the nested case study methodology suggested in **Chapter 4**, and a suggestion was made regarding further exploration of this in a future trial.

The calculation of a **sample size for a future trial** was provided for completeness. However, the calculation should be interpreted with caution due to its use of a within-participant CID. Many qualifying factors should also be taken into account, including the recommendation to use a minimum clinically important difference (MCID) informed by a PPI panel; the trial's unequal allocation ratio; the effect of pragmatism and the consequent heterogeneity of every aspect of PICO leading to the potential for increased sample size; and the effect of potential clustering by practitioner in reducing statistical power, with consequent effects on sample size. This section made an overriding recommendation to recalculate the sample size for a future trial based on a limited-scope feasibility study nested at the outset of a future trial, which would bring together clinicians, researchers, statisticians and patients to inform sample size as a workable compromise between MCID, power and generalisability of a future trial's results to real-world contexts.

8.1.2 Strengths of this feasibility study

This study's chief contribution to knowledge lies in aspects of its design leading to original findings that can inform a future large-scale trial investigating the effects of acupuncture and nutritional therapy on symptoms and HRQoL in AF.

Some findings may also be generalisable to future feasibility studies or large-scale pragmatic trials investigating these or other complementary therapies for other conditions and/or other outcomes.

The study has also proposed an extension to the existing pragmatic randomised controlled trials methodology – the nesting of case studies/case series within the trial – that may be able to produce a more nuanced representation of interventions' effects at individual trial participant level to augment the trial-level findings. This may be a useful strategy when investigating the effects of individualised holistic therapies.

Key contributions to original knowledge are:

- Determining the feasibility of investigating two individualised holistic therapies as practised in real-world contexts (as far as possible within limitations imposed by trials methodology

and ethics). A future trial would be the first of its kind in the AF area, and would have a high degree of generalisability to real-world contexts;

- Determining the feasibility of investigating nutritional therapy (NT) as a therapeutic approach for AF. A future trial is thereby positioned as the first large-scale randomised controlled trial of nutritional therapy in an AF population, and will be able to provide valuable data on this therapy's effectiveness for this population;
- Reporting on the safety of NT the context of AF. A future trial would provide valuable safety data to inform future investigational studies of NT;
- Determining several aspects of future trial feasibility in relation to private practitioners of acupuncture and NT;
- A consideration of the impact of the COVID-19 pandemic on the feasibility of investigating real-world acupuncture and NT.

8.1.3 Weaknesses of this feasibility study

This feasibility study had several inherent weaknesses, including limitations that have restricted generalisability to a future trial, and significant biases that may have influenced its results.

The most substantial **limitations** of this study included its status as a single-centre study; and the inability to blind its main outcomes assessor. The systematic review positioned at the outset of the study may have failed to identify some trials of complementary therapies for AF, and may have introduced biases in selection and data extraction due to having a sole reviewer.

Limitations introduced by budget included absence of funding for supplementation in the NT group, and the inability to fund a larger subset of participants wearing CardioSTAT® monitors. Limitations were also imposed by nutritional therapy itself, as a relatively young therapeutic discipline, due to current fluidity in professional parameters that may have resulted in the version of NT practised in the trial being unrepresentative of the therapy as practised in real-world contexts. A final general limitation, currently poorly defined due to novelty, is the current shift in thinking around the pathophysiology of AF and its causal link with sequelae, including stroke. This could not be explored within the scope of the feasibility study, but its potential impact on a future trial has been discussed.

Limitations in the scope and design of this study also affected the ability to address some key areas of uncertainty that may materially affect a future trial:

- The feasibility study detected **participant preferences** to an extent suggestive of both feasibility issues (recruitment, retention, acceptability of intervention) and potential bias (treatment effect, especially in the context of self-reported outcomes) for a future trial. A number of mitigating methods/designs have been discussed, but these could not be

investigated within the current feasibility objectives and design. A decision to use an alternative study design to take account of preferences in a future trial would generate considerable further uncertainty and should, if adopted, be the subject of a further feasibility study.

- The **restricted scope of practice of nutritional therapy**, if mirrored in a future trial, may render the results less generalisable to real-world contexts. Recommendations were made to extend the scope of nutritional therapy in a future trial.
- Questions were raised regarding **the inability of an RCT to optimally reflect real-world practice** for two interventions delivered in private practice. The private practice context is associated with a high degree of patient choice; in particular, its requirement for payment at the point of delivery may be associated with influence on treatment effects. These questions were beyond the remit of both the trial and this thesis.
- A range of limitations was imposed by **COVID-19**, including the restriction of follow-up to a single point at end of treatment; and a substantial change in the mode of delivery of nutritional therapy and the conduct of study assessments. A future trial that discards the COVID-19 modifications made to this feasibility study therefore retains a level of uncertainty in the feasibility of objectives relating to these areas.

The most substantial **biases** in this study included selection bias introduced by the eligibility criteria; Hawthorne effects in the practitioners; and biases relating to the single-centre status of the study including those relating to practitioner recruitment.

Potential biases that may reasonably be suspected but could not be reliably detected within the remit of this feasibility study include confirmation and observer bias relating to the work of a sole researcher (who was also a practitioner of one of the study interventions although not delivering any treatments in the study); behavioural biases for participants, including Hawthorne effects and cognitive measurement biases potentially affecting self-reported outcomes, particularly those arising from preferences in relation to group allocation and “obsequiousness bias”; and adherence bias generated by differential effects of patient-practitioner relationships.

Recommendations to mitigate all these biases in a future trial have been made in **Chapter 7**.

8.1.4 Further research

Chapter 3 highlighted a need for further investigational research into complementary therapies, as practised in real-world settings, for symptoms and HRQoL in atrial fibrillation. The systematic review also recommended that the range of effect modifiers identified in the review should be collected, reported, and used as covariates in analyses in future trials of interventions for AF.

This thesis as a whole recommends a future randomised controlled trial to investigate the effects of acupuncture and nutritional therapy for symptoms and HRQoL in atrial fibrillation. Additional sub-studies have been suggested above, to investigate the effects of treatment expectation and the effect of levels of adherence to self-care/lifestyle advice over a longer-term follow-up than the three months investigated by this study. Additionally, this study recommends the adoption of nested case studies/case series within the trial, using mixed methods to provide individual-level and group-level understandings of treatment effects.

Other findings from this study have nuanced the quantitative judgement of feasibility, revealing several issues that, while not affecting operational feasibility, may influence the generalisability and reliability of results in a future trial, and may therefore be considered at the design stage of a future trial. These are discussed below.

8.1.4.i The effect of preferences

The feasibility study revealed evidence of participant preferences in relation to interventions. Preferences may influence a range of variables in a future trial including adherence and treatment effects. Further research is therefore recommended into the effects of participant preferences on a range of trial parameters, including adherence and treatment effect, for the two therapies under investigation. This may be accomplished by redesigning a future trial to take account of preferences, either by using a preference design as described above, or by modifying the statistical methods of a future trial to identify preferences as covariate in pre-specified analyses.

The effect of preferences may also be inflected by considerations of pragmatism and the generalisability of a future trial's findings to real-world contexts, specifically with regard to the private provision of both therapies in such real-world contexts. Private provision, with its high degree of patient choice and requirement for payment by the patient at the point of delivery, may have a strong influence on trial variables such as adherence and treatment effects; trials of acupuncture and nutritional therapy may find it useful to incorporate these covariates in analyses. However, it would be ethically challenging to study the effect of these real-world parameters on treatment outcomes and adherence using a trial methodology.

8.1.4.ii Scope of nutritional therapy

As discussed above, the scope of nutritional therapy practised in this feasibility study was limited, and may not be representative of the therapy as practised in a real-world context. Further research is recommended to determine the scope of real-world practice, including the extent to which online working is now considered a standard practice. This research may take the form of a UK-wide or international cross-sectional survey in collaboration with one or more professional bodies and/or NT

educational standards bodies, with the results allowing closer and more accurate specification of NT parameters in a future trial.

8.1.4.iii Extension to pragmatic RCTs to accommodate "truly" complex interventions

The extension to pragmatic trials methodology suggested in **4.1.3.iv**, whereby case studies/series of individual participants are nested within a traditional pragmatic trial, represents an area for future methodological development. A possible development pathway is outlined in **7.8.6.ii** and may prove supportive for future investigations of individualised holistic therapies as defined by this thesis.

8.1.5 Feasibility of a future trial

This feasibility study has demonstrated the feasibility of six of its total 10 feasibility domains. Of the remaining four, two (the CardioSTAT® feasibility analyses) were inappropriate or unviable, while recommendations were made to increase feasibility of a third (percentage of identified participants eligible). The final domain (participants' report of assessment acceptability) failed to meet its feasibility threshold due to participant error; when the error was corrected, the threshold was met.

The study also made a range of additional recommendations to increase the reliability and generalisability of a future trial's results to real-world contexts.

The study has therefore determined that a future trial using the design of this feasibility study is overall feasible; and may achieve greater reliability and generalisability if it adopts some of the additional recommendations set out above.

Appendix A: General trial and study documentation

This material was too large to include as an Appendix. Instead, it has been uploaded to the online repository Open Science Framework, where it can be viewed and downloaded.

Protocol and ethics

Study protocol: **https://osf.io/kexra**

Ethics approval, University of York HSRGC, July 2019: **https://osf.io/4x3mf**

Ethics approval, 3rd November 2020: **https://osf.io/4b3qn**

Substantial amendment (1) approval, 7th May 2021: **https://osf.io/nuvw9**

Non-substantial amendment (2) approval, 23rd August 2021: **https://osf.io/rafpt**

Substantial amendment (3) approval, 6th January 2022: **https://osf.io/snbyr**

Non-substantial amendment (4) approval, 29th March 2021: **https://osf.io/4taeq**

Practitioner documents

Practitioner eligibility questionnaire: **https://osf.io/n3exw**

Practitioner training workshop slides (all) (PowerPoint file): **https://osf.io/ru375**

Practitioner training workshop slides (acupuncturists) (PowerPoint file): **https://osf.io/9ynqf**

Practitioner training workshop slides (NTs) (PowerPoint file): **https://osf.io/qw4yb**

Practitioner study manual (acupuncturists): **https://osf.io/qkucf**

Practitioner study manual (NTs): **https://osf.io/uzd9t**

Practitioner log book (acupuncturists): **https://osf.io/8rtzj**

Practitioner log book (NTs): **https://osf.io/9xdjf**

Practitioner exit interview topic guide (acupuncturists): **https://osf.io/qnw8t**

Practitioner exit interview topic guide (NTs): **https://osf.io/ps9cv**

Practitioner legal agreement (acupuncturists, blank): **https://osf.io/2fsut**

Practitioner legal agreement (NTs, blank): **https://osf.io/psgmb**

Participant identification and randomisation

PIC search/screen log (participant identification) (Excel file): **https://osf.io/u7264**

Sample randomisation confirmation email (participant 2/136/UC): **https://osf.io/84pru**

CardioSTAT® randomisation (Excel file): **https://osf.io/yja8u**

Maximum variation sampling strategy for interview (Excel file): **https://osf.io/j9dz2**

Trial Steering Committee

Terms of Reference: **https://osf.io/7mghn**

Minutes of meeting held 10th November 2021: **https://osf.io/m28as**

Funding and costings

BAcC funding confirmation and COI rebuttal: **https://osf.io/ktqbu**

Validated SoECAT, 9th June 2021 (Excel file): **https://osf.io/yptsa**

Study outline costings (final): **https://osf.io/gm3ud**

Miscellaneous

BANT funding application rejection: **https://osf.io/sq5ef**

Notes of discussions held with NCA colleagues re. capacity: **https://osf.io/5d7cs**

Objectives survey and progression thresholds (Excel file): **https://osf.io/rqnwm**

Study newsletter, Winter 2021: **https://osf.io/3mr95**

AFEQT licence agreement: **https://osf.io/kvzrq**

Researcher's positionality statement: **https://osf.io/4xdyn**

Feasibility study methodology literature (Excel file): **https://osf.io/spqhx**

Appendix B: Recruitment material

Click the document name to jump to it within this Appendix.

Permission to Approach pack (5pp)

Download whole document from: **https://osf.io/grk3a**

Participant Information Sheet (22pp)

Download whole document from: **https://osf.io/g2zc6**

Consent Form (4pp)

Download whole document from: **https://osf.io/cdq84**

Permission to Approach (PtA) pack: Introductory letter

Santé-AF Sessions of Acupuncture and Nutritional Therapy Evaluation for Atrial Fibrillation
Feasibility study to inform a randomised controlled trial

25th September 2021

Dear

Introducing Santé-AF – study participation

I am writing to ask if you would like to find out more about a new research study, known as Sessions of Acupuncture and Nutritional Therapy Evaluation for Atrial Fibrillation (Santé-AF for short). The researchers are looking to find out whether traditional acupuncture or nutritional therapy can help people with atrial fibrillation have fewer symptoms and a better quality of life. At this stage, they are conducting a small-scale study to see if a larger-scale trial is feasible. **Please note that the study has been designed to be as safe as possible with regard to COVID-19.**

We think that you may be interested in participating in this small-scale study, because you have been diagnosed with atrial fibrillation.

Qualified medical professionals at this practice have carefully screened your record to identify this information. Please be assured that **this has been done in strict confidence**: only authorised healthcare professionals have accessed your records. Unless you return the enclosed form to the researchers, telling them that you would like to be sent more information, they will remain entirely unaware of your identity.

If you are not interested in taking part, you need do nothing further. But if you are interested, we have enclosed some brief details to help you decide whether you would like the researchers to send you more information about this study.

Thank you for reading.

HRA/HCRW & NHS REC ref: 20/LO/0598 | IRAS Project ID: 268585 | ISRCTN13671984

University of York

nca Northern College of Acupuncture

4 Introductory letter, v1.2 | 31/12 /20

Permission to Approach (PtA) pack: Basic Study Information Sheet p1/2

Santé-AF Sessions of Acupuncture and Nutritional Therapy Evaluation for Atrial Fibrillation

Feasibility study to inform a randomised controlled trial

Basic Study Information Sheet

Version 1.2 – Date 31 December 2020

We would like to invite you to take part in a research study

- To help you decide whether you wish to be contacted with more information, we would like to ask you to read this document. It will give you some basic information about the study.
- If you decide you would like to be contacted with more information, please fill in the form with this leaflet, and return it to us in the envelope provided. We will send you more information by post.

What is this study about?

This is a research study to help us find out whether acupuncture or nutritional therapy are helpful for people with atrial fibrillation (AF).

We want to do a large trial to see if people with atrial fibrillation have fewer symptoms and a better quality of life if they have a course of acupuncture treatment or nutritional therapy consultations.

First, we need to do a smaller study to see if a large trial is possible. You are being contacted about this smaller study.

Why am I being contacted?

Medical staff at your GP practice have identified from your medical records that you may be eligible to take part in the study. This information has been gathered in strict confidence by these staff, and will not be shared with the researchers unless you decide to take part in the study.

What is involved in taking part in the study?

All participants in the study are randomly placed into one of three groups:

- The first group (12 people) will receive up to eight traditional acupuncture treatments along with their usual NHS treatment for AF, over 8-10 weeks. There is a 40% (2 in 5) chance of being placed in this group. These appointments will be held face-to-face at private acupuncture practices in or close to York city centre. Acupuncturists operate under a strict code of safety regarding COVID-19 including wearing of PPE (you must also wear a mask), thorough cleaning before and after each appointment, and checking your COVID status before you arrive;
- The second group (12 people) will receive up to three nutritional therapy consultations along with their usual NHS treatment for AF, over 8-10 weeks. There is a 40% (2 in 5) chance of being placed in this group. These appointments will be held online to minimise the risks of COVID-19;
- The third group (6 people) will receive only their usual NHS treatment for atrial fibrillation. There is a 20% (1 in 5) chance of being placed in this group. People in this group will have no extra appointments in addition to their usual NHS AF-related appointments.

No matter which group they are placed into, all participants are asked to do two assessments. These will be done online due to COVID-19. If you do not have a device with video calling software, the study will lend you an iPad and guide you on how to use it. The first assessment will be at the start of the study and the second will be about three months afterwards. During the assessments, participants will be asked to fill in a questionnaire and guided by the researcher to take some measurements. This will take about 40 minutes each time.

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Please turn over

HRA/HCRW & NHS REC ref: 20/LO/0598 | IRAS Project ID: 268585 | ISRCTN13671984

Permission to Approach (PtA) pack: Basic Study Information Sheet p2/2

A third (33%) of participants will be randomly selected to wear a CardioSTAT™ heart monitor for 7 days, twice over the course of three months. All participants, whatever their group, have a 33% chance of being selected to wear the monitor. The CardioSTAT™ is a small device temporarily attached to the chest to monitor AF symptoms while you go about your normal life. If you are selected to wear a monitor, to minimise the risk of COVID-19 we will send this to you and you will be guided to fit this yourself, during your assessment appointment. At the end of 7 days you will be asked to remove it and send it by Freepost to a laboratory, which will analyse the data and share it with your GP and the researcher.

We will also ask participants if they are willing to be interviewed about their experience of taking part in the study. Participants do not have to be interviewed if they do not wish. If participants are willing to be interviewed, we will randomly select the interviewees and carry out the interviews online, during the online assessments.

What are acupuncture and nutritional therapy?

In an acupuncture treatment, the acupuncturist will ask detailed questions about your health (not just your AF) and make a diagnosis according to the principles of Traditional Chinese Medicine. They will insert small, fine needles at acupoints to restore balance to your system, which may address your AF symptoms and help you feel better overall. With your consent, they may also use other treatments such as acupressure massage, gentle electrical stimulation of the needles, burning a Chinese herb called moxa close to the skin, or seeds/magnets on pressure points. They will also offer you advice on self-care such as diet, exercise and relaxation.

In a nutritional therapy consultation, your nutritional therapist will ask detailed questions about your health (not just your AF) and about your diet. They will analyse this information and write a dietary plan intended to address your symptoms and help you feel better overall, and they will support you to follow this plan. They may also offer you advice on self-care such as exercise and relaxation.

What are the benefits and disadvantages of taking part?

We cannot promise that the study will definitely help you, as an individual, reduce your AF symptoms, feel better or improve your self-care; but the information we get from this study will help to answer the question of whether people with AF having acupuncture or nutritional therapy do better than people who are not having these therapies. If you take part in the study, you are contributing to our knowledge about a range of different treatments for AF.

There are no costs involved in taking part in the study. If you are attending acupuncture appointments, we will pay £5 for each appointment to help meet your travel costs. All participants will receive a £10 retail voucher on completing the final assessment.

Do I have to take part?

Participation in this study is entirely voluntary. You may refuse to participate or withdraw from the study at any time, and your usual care will not be affected in any way whatsoever.

What do I do next?

If you do not wish to be contacted with more information about the study, you need do nothing further. We will not contact you again. We would be very grateful if you could let us know more about why you do not wish to take part, *although you do not have to do this*. There is space on the enclosed form for you to tell us this anonymously, if you wish to.

If you would like to be sent more information about the study, please fill in the enclosed form and return it to us in the envelope provided. We will send you more information by post.

If you give us permission to send you more information, this does not mean we will enrol you in the study. We will only send you more information to help you decide whether to take part.

Thank you for reading this Basic Study Information Sheet.

8 Sante-AF basic SIS, v1.2 | 31/12/20

Permission to Approach (PtA) pack: Permission to Approach form p1/2

Study ID:

Santé-AF Sessions of Acupuncture and Nutritional Therapy Evaluation for Atrial Fibrillation
Feasibility study to inform a randomised controlled trial

PIC code:

Permission to Approach Form

Version 1.2 – Date 31 December 2020

If you would like to receive more information about the Santé-AF study, please put your initials in the boxes below, complete the contact details section, and then sign and date this form. Please return it to the Northern College of Acupuncture in the envelope provided.

Please initial ALL boxes

1. I confirm that I have read and understood the basic Study Information Sheet version 1.2 dated 31 December 2020 for the above study, and **I am interested in receiving more detailed information** so I may decide whether or not to take part in the study. I understand that by giving this permission to approach, **I am not consenting to take part in the study at this stage**. I am only agreeing to receive more information about the study to help me decide whether to take part. I may refuse to take part in the future. — your initials

2. **I agree to the researcher holding a copy of this Permission to Approach form** to demonstrate that I have given permission to send more information. I understand that the information I give in this form will be securely stored and destroyed 10 years after the end of the study. I understand that this information will not shared in identifiable form with anyone outside the study, whether or not I agree to take part in the study, in accordance with GDPR and the Data Protection Act (2018). — your initials

3. **I would like to receive more information about the Santé-AF study.** — your initials

Now, please turn over...

If you prefer NOT to receive more information about the Santé-AF study (you do not want to take part) please TICK this box: please tick

We would be very grateful if you could tell us briefly why you do not want to receive more information about the study, or take part. **You do not have to do this**, but if you do, it will help us to design a better study in future. You can write here:

Thank you. Please return this form in the envelope provided – we will not contact you again.

University of York — nca Northern College of Acupuncture

NHS HRA REC reference: 20/LO/0598 | IRAS Project ID: 268585 | ISRCTN13671984

Santé-AF, c/o Northern College of Acupuncture
61 Micklegate, York YO1 6LJ • 01904 343305

Permission to Approach (PtA) pack: Permission to Approach form p2/2

Your contact details

Please do not complete this section if you have told us on the previous page that you do not want to receive more information or take part in the study.

Your first name(s):

Your surname:

Your title *(please circle your preference)*:

Mr / Mrs / Ms / Miss / Other, please state:

House name/number:

Street/road:

Town/city:

Postcode:

Please give your email address:

Please give your contact phone number (this can be a mobile number if you wish):

Your signature

Please do not complete this section if you have told us you do not want to receive more information or take part in the study.

To give us your permission to send you more information about the study, please sign and date below:

Signature

Signature of participant *(please SIGN your name)*

Print name

Name of participant *(please PRINT your name)*

D D M M Y Y Y Y

Date

Please return ONE COPY of this form to the Northern College of Acupuncture in the envelope supplied. The other copy is for you to keep.

9 Sante-AF permission to approach, v1.2 | 31/12/20

Santé-AF, c/o Northern College of Acupuncture
61 Micklegate, York YO1 6LJ • 01904 343305

Participant Information Sheet: p1/22

Santé-AF Sessions of Acupuncture and Nutritional Therapy Evaluation for Atrial Fibrillation

Feasibility study to inform a randomised controlled trial

Participant Information Sheet

Version 1.4 – Date 26 January 2021

We would like to invite you to take part in a research study

- To help you make an informed decision, we would like to ask you to read this document.
- Please do not hesitate to contact us to ask for further information at any time (contact details are on the final page).
- Please feel free to discuss any of this with your family and friends.

What is the purpose of this study?

Research shows that people living with atrial fibrillation (AF) feel they have a lower quality of life than people who do not have AF. People with AF also report that as their level of symptoms increases, their quality of life decreases.

We want to do a large trial to see if people with atrial fibrillation experience a change in their symptoms and/or their quality of life if they have acupuncture or nutritional therapy.

First, we need to do a smaller study to see if a large trial is possible. You are being invited to take part in this smaller study.

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2 Why have I been invited?
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Extra information

You do not have to read this, but it may provide helpful information

16 A guide to online assessments
20 Study roadmap

University of York | nca Northern College of Acupuncture

HRA/HCRW & NHS REC ref: 20/LO/0598 | IRAS Project ID: 268585 | ISRCTN13671984

Participant Information Sheet: p2/22

Why have I been invited?

You have been invited to participate in this study because your medical care team at your GP surgery have identified from your medical records that you have been diagnosed with atrial fibrillation, at least six months but less than five years ago, and that you are at least 45 years old (but under 70). Your AF care team have also checked your records to make sure that you have been offered all the appropriate medical care for your AF, and that you are not classified as clinically vulnerable in relation to COVID-19, before you were contacted about this study.

At this stage, we do not know if you are fully eligible to take part. To take part, you will need to meet the eligiblity conditions set out below (please see **How will I know if I am eligible to take part?** below). We will check and let you know if you are eligible to take part.

How will I know if I am eligible to take part?

To take part in this study, you need to meet the following conditions:

- You must be aware of your AF when it happens, and it should happen at least once a week (even if you are taking AF medication or have had any hospital treatments for your AF). This may mean that you feel unusually breathless, or have palpitations, fatigue, dizziness or fainting, or have chest discomfort;
- You must be willing to have either acupuncture or nutritional therapy alongside your usual care (your medications or other NHS treatments for AF);
- You must be willing to do two assessments: one at the start of the study, and one after about three months. Please note that, due to COVID-19, all study assessments will be carried out online. You will be guided to carry out the assessments, which involve taking some measurements and filling in some forms. Please see **What will happen at the online assessments?** on page 4, and the separate section **A Guide to Online Assessments** on pages 16-19 for more information about assessments;
- If you are randomly allocated to the Acupuncture group, you must be willing to travel to your acupuncture appointments (weekly over an 8–10 week period). We will pay you £5 per appointment to help meet your travel costs;
- If you are randomly allocated to the Nutritional Therapy group, you must be willing to attend nutritional therapy appointments (approximately once a month for 3 appointments). These will be carried out online to minimise the risk of COVID-19. You will be guided through the process of attending appointments online;
- You must be willing and able to use your own mobile phone and email address to receive and respond to text messages, phonecalls and emails about the study;
- You must have a computer, tablet or smartphone with Microsoft Teams OR be happy to use the study iPad (with guidance from the researchers) to do online assessments. Please see the section **A Guide to Online Assessments** on page 16-19 for more information about this;
- You must have a home broadband connection in a quiet, private room where you can do the online study assessments, twice in a 10-12 week period;

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- You must be able to speak and write English well enough to talk with your acupuncturist or nutritional therapist without help from anyone else, and to complete the questionnaires we will give you without help from anyone else. This is because the study does not have the resources to fund translators or interpreters;
- You must be able to give your informed consent without help from anyone else.

You will NOT be able to take part in the study if you:

- Have a condition that might make it inadvisable for you to take part – such as advanced kidney disease, a blood clotting disorder, an eating disorder, any terminal or life-limiting illness, or any condition that means you should not do suitable moderate exercise;
- Have any of the following fitted: a pacemaker, an implanted defibrillator, a neurostimulator or any other type of active implantable device;
- Are regularly using a TENS machine or receiving any regular diathermy, diagnostic or therapeutic ultrasound, radiation therapy, electrosurgery or x-rays;
- If your AF is related to your heart valves ("valvular AF"), or if it is officially diagnosed as "permanent", which means that it happens all the time;
- Are pregnant or trying to conceive;
- Are shielding, or classified as either clinically vulnerable or clinically extremely vulnerable to COVID-19, according to NHS advice; or if you are living with or bubbled with anyone in any of these categories;
- Are taking part in any other medical research that might affect the results of this study, or which might affect your safety if you enter this study in addition.

If I am eligible, what will happen next?

Using the details you gave us on the Permission to Approach form, we will telephone you in the next few days to ask whether you have any questions about the study. When we have answered those (or if you don't have any questions), then if you would like to take part in the study you should sign and return to us one copy of the Consent Form in the envelope provided.

When we receive your signed Consent Form, we will telephone you again – this time to ask some questions to check that you are fully eligible to take part (the "screening phonecall"). We will then invite you to attend a first online assessment (a "baseline assessment"). Please see **What will happen at the online assessments?** (page 4) for information about the assessments and what we will ask you to do.

If this second phonecall reveals that you are NOT eligible to take part, we will send you a letter to let you know this. We will securely store the information you have given us so that we can show why you are not eligible to take part. In the study write-up, we will report anonymously all the reasons that people were not eligible. You will not be publicly identifiable in any way. We will securely destroy this information after 10 years.

We have put more details about the progress of the study in the **Study Roadmap**, on page 20-21 of this information booklet. Please read this for more information about how the study will progress, what we will ask you to do, and when we will ask you to do it.

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What will happen at the online assessments?

We will ask you to do two assessments. One will be at the start of the study, and the second will be about three months after the start of the study. Both assessments will be identical, although the questionnaire will be slightly different at each assessment.

To minimise the risk of COVID-19, we will carry out all assessments online. The researcher will stay online with you throughout the assessment. Please read the section **A Guide to Online Assessments** on page 16-19 for more information about online assessments.

In each online assessment, we will ask you to:

- **Record details of your current medications.** If you prefer, you can simply show your medication bottles and boxes to the camera. The researcher will write down the names and dosages.
- **Take away an AF symptom diary sheet to complete over the next 7 days.** We will give you an AF symptom diary sheet, so you can write down your AF symptoms over the following 7 days. We will give you a stamped envelope to return this in the post.
- **Tell us your height.**
- **Fill in a questionnaire** about your health, personal information and AF, your ways of taking care of yourself, and your quality of life. We will also ask you about your COVID/vaccination status, and your feelings about taking part during a pandemic.
- **Interview you about your experience of having AF and your experience of taking part in the study.** If you have told us you are willing to be interviewed about these things, we will also carry out your interview at this appointment. The interview should last no longer than 40 minutes, in addition to the 40 minutes of other activities above. Please note that we cannot interview everyone who is willing, due to time constraints.
- **Measure your weight, your waistline, your hip circumference and your blood pressure.** We will provide equipment for you to use, and we will guide you through the process of taking these measurements. You can turn the camera off for these sections, if you prefer.
- **Fit a CardioSTAT® heart monitor** to your chest, with guidance (if you have been randomly selected to wear one). Please see **What is the CardioSTAT® heart monitor?** on page 7 more information. If you have been selected to wear a CardioSTAT®, we will deliver it to you, and we will guide you to fit this during your online assessment.

When we have gathered all the data from your second assessment, we will give you a £10 retail voucher as thanks for your time. Please see **Will it cost me money to take part in the study?** on page 8 for more information about what we will pay you and how we will pay it.

After the first online assessment, what happens next?

After we have collected all your baseline data, and you have returned your AF diary sheet (and CardioSTAT® if you are selected to wear one), we will enrol you in the study. This means you will be randomly placed into one of three study groups: Acupuncture, Nutritional Therapy or Usual Care. The researchers have no control over which group you are placed in.

Participant Information Sheet: p5/22

We will write to you, to let you know which group you have been placed in. If you have been placed in the Acupuncture or Nutritional Therapy groups, we will send you details of the acupuncturist or nutritional therapist who will be working with you, and we will ask you to contact them to make your first appointment at your own convenience. If you have been placed in the Usual Care group, you will simply continue with your usual treatment for AF as given by your GP or your cardiologist.

Please feel free to call us at any time to ask any questions you may have regarding this study. You can find contact details at the end of this Information Sheet.

There are three private acupuncturists and three private nutritional therapists working on the Santé-AF study. You may be assigned to receive treatment from any of these practitioners. If you are unhappy with the choice of practitioner assigned to you, please let us know **before your first appointment**, because we may be able to change this – but we can only do this before your first appointment, so it is important to get in touch with us straight away. You do not have to give any reasons for wanting to change your assigned practitioner, and the practitioner will not be told of your decision to change.

Whatever group you have been placed in, we will send you two text messages to ask how satisfied you are with your allocated treatment, and whether you expect your AF to improve, stay the same, or get worse during the study.

What are the three groups in the study?

The three groups in the study are:

- Group A: Acupuncture + Usual Care
- Group B: Nutritional Therapy + Usual Care
- Group C: Usual Care.

Everyone taking part in the study will continue with usual care (their existing NHS treatment for AF) no matter what group they are placed into. People placed into the Acupuncture or Nutritional Therapy groups will receive acupuncture or nutritional therapy *as well as* their existing NHS treatment. **It is very important to continue with your usual care while you are in the study.**

See **What are acupuncture, nutritional therapy, and usual care?** on page 6 for details of each kind of treatment in the study, and what they involve.

You are asked to continue with your usual care for AF (in addition to having acupuncture or nutritional therapy appointments if you are allocated to one of these groups). **It is very important that you do not make changes to your usual care (except any changes made by your NHS care team).**

Please note that while we will monitor changes in your AF as part of the study, we will do this for research purposes rather than for the purposes of your medical care. This means that data may not be analysed promptly. **It is very important that if you become aware of any changes in your health that are of concern to you, you must get in touch with your care team straight away.**

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What are acupuncture, nutritional therapy, and usual care?

Group A: Acupuncture

If you are randomly placed into the Acupuncture group, you will have up to eight weekly sessions of acupuncture with a traditional acupuncturist while continuing with your usual treatments or medications for AF. Your acupuncturist will ask detailed questions about your health (not just your AF) and make a diagnosis according to the principles of Chinese medicine. They will insert small needles at acupoints to restore balance to your system. They may also use other treatments such as acupressure massage, burning a Chinese herb called moxa close to the skin, electro-acupuncture using a low electrical current, or seeds/tacks on ear pressure points. They will also offer you advice on self-care areas such as diet, exercise and relaxation.

A first appointment may take up to 1.5 hours, and every following appointment will take about an hour.

Group B: Nutritional Therapy

If you are randomly placed into the Nutritional Therapy group, you will have up to three online consultations with a nutritional therapist while continuing with your usual treatments or medications for AF. Your nutritional therapist will ask detailed questions about your health (not just your AF) and about your diet. They will analyse this information and write a dietary plan specifically designed for you. They may also offer you advice on self-care areas such as exercise and relaxation.

They will send this dietary plan to you and you will be able to discuss it with them at your second appointment. At a third appointment, they will check how you are getting on and make any adjustments to the plan that you need.

A first appointment may take up to 1.5 hours, and every following appointment will take about an hour.

Group C: Usual Care

If you are randomly placed into the Usual Care group, you will continue with your existing NHS treatments or medications for AF. These include:

- **medications** including anticoagulation and/or anti-arrhythmic drugs or drugs to control your heart rate and rhythm;
- **electrical cardioversion**, which is a controlled electrical shock to the heart to restore normal rate/rhythm;
- **catheter ablation**, which is a minimally-invasive procedure to remove parts of the heart tissue that are thought to cause AF.

COVID-19 safety in the Santé-AF study

We have taken the following actions to minimise the risk of COVID-19 transmission during appointments:

Nutritional therapy appointments will be held entirely online with no face-to-face meetings.

Acupuncture appointments have been made as safe as possible. Acupuncturists in the Santé-AF study are all members of the British Acupuncture Council and they are required to follow a COVID-19 code of safety. This covers a full range of measures including increased hand hygiene by participants and acupuncturists, the use of full PPE by acupuncturists, and thorough cleaning of all surfaces and ventilation of rooms between patients. Patients will also be asked to wear masks to their appointments (unless there is a medical reason for not doing so), and to confirm COVID status immediately on arrival.

Please ask if you have any questions regarding the COVID-19 safety of the study. Contact details can be found on the back cover of this information leaflet.

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Will I definitely get acupuncture or nutritional therapy?

Every person taking part in the Santé-AF study has a 4 in 5 (80%) chance of being randomly selected to receive *either* acupuncture *or* nutritional therapy.

There is a 1 in 5 (20%) chance of being randomly selected to receive usual care, in which you won't receive either acupuncture or nutritional therapy, but will continue with your usual care as given by your GP or your cardiologist.

If you are placed into the Usual Care group, you are still playing an extremely important role in the study. This is because we need to compare the groups to find out whether acupuncture or nutritional therapy change symptoms and quality of life. So if you are placed in the Usual Care group, **it is vital that you do your online assessments**, and complete the 7-day AF diaries we will give you during the study, including wearing a 7-day CardioSTAT® heart monitor twice if you are selected to do this. By doing this, you are playing an essential role in helping us to discover if acupuncture and nutritional therapy have an impact for people with AF.

The study administrators have no control over which group you are placed in, or whether you are selected to wear the CardioSTAT® heart monitors.

Please feel free to call us at any time to ask any questions you may have regarding this study. You can find contact details at the end of this Information Sheet.

What is the CardioSTAT® heart monitor?

The CardioSTAT® is a small electrocardiograph (ECG) heart monitor that you wear while going about your normal life. It measures your heart activity and collects data on your AF symptoms.

One-third of the people enrolled in this study will be randomly assigned to wear a CardioSTAT® monitor. If you are one of these people, you do not need to make any changes to your daily activities while you are wearing it (in fact, it is important that you continue everything as normal). You can wash and shower as usual. After 7 days, you will be asked to remove the CardioSTAT® and send it back by freepost to Icentia, the manufacturers of CardioSTAT®, who will analyse the data in their laboratory and share it with the researchers and your GP.

The data collected by the CardioSTAT® will be 'pseudonymised', meaning that it is given a code which does not connect it with your identity. Your data will also be made available in pseudonymised form to the researcher, so it can be included in the study (see **Confidentiality and Data Protection** on page 10 for more information).

Every person taking part in the Santé-AF study has a 1 in 3 (33%) chance of getting a CardioSTAT® heart monitor, no matter what group they are randomly placed into. This includes the Usual Care group.

CardioSTAT® is manufactured by a Canadian company called Icentia Inc., whose UK arm, Icentia Limited, is based in York at the Science Park next to the University. You can find out more about Icentia by visiting **https://www.icentia.com/home** and you can find out more about the CardioSTAT® monitor here: **https://www.cardiostat.com/uk/home.** Alternatively, you can get in touch with the researcher to ask more questions about the CardioSTAT®. Contact details can be found at the end of this Information Sheet.

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What is my total time commitment to the study?

You will be involved in the study for a total of approximately 4 months. This includes everything from the time you agree to take part, up to the time you attend for your final online assessment.

Below we have set out a table showing how much time you will need to give to the study, over the course of 4 months.

The **Study Roadmap** (page 20-21) gives an at-a-glance summary of the study progress. Please read this for a summary of how the study will move forward, what we will ask you to do, and when we will ask you to do it.

Group A: Acupuncture

If you are randomly placed into the Acupuncture group, your total time commitment during the 4 months will be:

- About **one and a half hours** to attend the assessments, plus a further **one and a half hours** to be interviewed (if you are willing to be interviewed, and you are selected for interview);
- About **nine hours** to attend your acupuncture appointments;
- **Travelling time** to and from your appointments.

Group B: Nutritional Therapy

If you are randomly placed into the Nutritional Therapy group, your total time commitment during the 4 months will be:

- About **one and a half hours** to attend the assessments, plus a further **one and a half hours** to be interviewed (if you are willing to be interviewed, and you are selected for interview);
- About **four hours** to attend online Nutritional Therapy appointments.

Group C: Usual Care

If you are randomly placed into the Usual Care group, your total time commitment during the 4 months will be:

- About **one and a half hours** to attend the assessments, plus a further **one and a half hours** to be interviewed (if you are willing to be interviewed, and you are selected for interview).

Will it cost me money to take part in the study?

There are no costs involved in taking part in the study, except:

If you are placed in the Acupuncture group, there is the cost of travelling to and from your appointments. We will pay you £5 for each appointment you attend, to help you meet your travel costs.

Are there any benefits to being involved?

If you take part in the study, you are contributing to our knowledge about future potential treatments for AF. This is the case even if you are placed in the Usual Care group and do not

Participant Information Sheet: p9/22

receive acupuncture or nutritional therapy. Our hope is that we can use the knowledge we gain in this study to help us design a larger trial that will produce high-quality evidence about whether these treatments change symptoms and quality of life for people with AF.

We cannot promise that the study will definitely change your quality of life or your symptoms; but the information we get from this study will help to answer the question of whether people with AF having acupuncture or nutritional therapy experience a change in their quality of life and/or their symptoms compared with people who are not having these therapies.

We will give you a £10 retail voucher as a thank-you for your time if you complete both assessments (at the study start, and after three months).

Can I continue with my therapy after the study has finished?

The study has no budget to pay for you to continue having either acupuncture or nutritional therapy after the study has finished. Any further treatment you choose to have after the end of the study would be at your own expense.

However, if you would like to continue having treatment after the study finishes, you will be offered the chance to attend the acupuncture or nutritional therapy clinics at the Northern College of Acupuncture, in central York. These are teaching clinics, offering low-cost acupuncture and nutritional therapy with support for lifestyle change.

Do I have to take part?

Participation in this study is entirely voluntary. You may refuse to participate or withdraw from the study at any time, and your usual care will not be affected in any way whatsoever. You do not need to tell us why you do not want to continue. (We will ask you, because it is very helpful to have this information – but you do not have to answer.)

If you withdraw, we will include in our analyses the information you have given us before your withdrawal, including publications. This information will be completely anonymised and you will not be identifiable in any way.

Are there any risks or burdens involved?

Risks of taking part in the study
There are minimal risks involved in participating in this study.

Acupuncture has a good safety record. Some patients (8.6%) report at least one unpleasant side-effect of acupuncture. For more than half these patients (6.1%) the most common issue is bleeding or haematoma (clotted blood under the skin), while others report pain. There is a risk of superficial bleeding or bruising, particularly if you are taking anti-coagulant drugs, but your acupuncturist is trained to take this into account and will adapt your treatment to maintain your safety. Some people may feel tired after treatments. Your acupuncturist will ask you about any effects you have noticed, and will monitor these carefully.

Nutritional Therapy does not have an established safety record. There is a risk that some dietary strategies may affect the action of anticoagulant medications, but to ensure your safety, nutritional therapists are not permitted to use such dietary strategies in this study. Your nutritional therapist will ask you about any effects you have noticed, and will monitor these carefully.

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If you tell the study researcher, or your therapist, about any symptoms that in their opinion may need further investigation, they will write to your GP to ask them to follow this up with you. These symptoms may not be connected with your atrial fibrillation.

In addition, if you are asked to wear the CardioSTAT® heart monitors, and the monitor detects any symptoms that may need further investigation, the researcher will write to your GP to ask them to follow this up with you.

COVID-19 safety in the Santé-AF study

We have taken the following actions to minimise the risk of COVID-19 transmission during appointments:

Nutritional therapy appointments will be held entirely online with no face-to-face meetings.

Acupuncture appointments have been made as safe as possible. Acupuncturists in the Santé-AF study are all members of the British Acupuncture Council and they are required to follow a COVID-19 code of safety. This covers a full range of measures including increased hand hygiene by participants and acupuncturists, the use of full PPE by acupuncturists, and thorough cleaning of all surfaces and ventilation of rooms between patients. Patients will also be asked to wear masks to their appointments (unless there is a medical reason for not doing so), and to confirm COVID status immediately on arrival.

Please ask if you have any questions regarding the COVID-19 safety of the study. Contact details can be found on the back cover of this information leaflet.

Burdens of taking part in the study

All people taking part in the study will experience some additional burden in completing the assessments (questionnaires and other measurements). We have tried to minimise this burden by:

- making the questionnaires as short and easy to understand as possible;
- providing one-to-one guided support throughout the assessments, to make them as easy to carry out as possible;
- providing technology and equipment to assist the online assessment process, to avoid anxiety or stress for participants.

Confidentiality and data protection

The UK Health Research Authority provides generic information regarding how your data is used in research. If you would like to see this, please visit: **bit.ly/hra-patient-data**. If you do not have access to the internet, please ask the researcher for a printed copy to be sent to you. You can find contact details on the last page of this Participant Information Sheet.

Please feel free to call us at any time to ask any questions you may have regarding this study. You can find contact details at the end of this Information Sheet.

Confidentiality

During your treatment period, your personal information, including information about your health that you choose to share, will be known to your acupuncturist or nutritional therapist – just as it would be if you were consulting them privately yourself. If your practitioner works in a multidisciplinary clinic (where more than one practitioner works at the same time), the clinic reception/management staff will have access to information such as your name and contact details, although they will not be able to access your personal health information.

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Some information from your consultations will be shared with the researcher, so that it can be included in the study analysis. Before it is shared, this information will be 'pseudonymised', meaning that it will be given a code instead of your name. All identifying details, such as your name and address, will be removed. All documents will be identified only by this code, and all analysis is carried out using the pseudonymised data, so that no data used in the analysis can be linked directly back to you. Your personal information will be kept strictly confidential, and will not be shared outside of the study.

The only exception to this is if you reveal information either to your acupuncturist or nutritional therapist, or to the researcher during your assessments, that suggests you may be a danger to yourself or to others. In this case your practitioner and the researcher have a duty of care to protect you and the public that overrides confidentiality requirements, and they will inform your GP. This duty of care will be explained to you in your first assessment with the researcher, and your first consultation with your acupuncturist/nutritional therapist.

In addition, if you report either to your acupuncturist or nutritional therapist, or to the researcher during your assessments any symptom which in their opinion may require further investigation, they will write to your GP to refer this matter to them. In addition, if the data from your CardioSTAT® heart monitor, when analysed by Icentia Limited, indicates any symptoms that may require further investigation, Icentia will report these symptoms to the study's consultant cardiologist, Dr Sanjay Gupta of York Teaching Hospital. He will in turn report this to your GP. Your GP may contact you to follow up any of these issues.

How we will use and store your data during the study
All documents, including the 'look-up table' that links your identifying details with your identification code, will be kept securely, either in a locked cabinet in a locked room (paper forms), or on securely managed servers at the University of York (electronic data). This is in accordance with the General Data Protection Regulations (GDPR) and the UK Data Protection Act 2018.

The researcher will use your name and contact details to:

- keep in touch with you about the study;
- inform your GP that you are involved in the study;
- pass relevant information gathered during the study to your GP (including data gathered from your CardioSTAT® heart monitor, if you are asked to use one).

In addition, data from the CardioSTAT® heart monitors (if you are asked to wear these) will be processed by the manufacturers, Icentia Limited. You are identified to Icentia only by a code, and processing will be carried out in strict confidence. Your CardioSTAT® data will be shared with your GP, with the study's consultant cardiologist, and with the researcher.

Additionally, we will use your name and mobile phone number to stay in touch with you, using an SMS messaging management service called FireText. FireText Communications Limited is a Government-approved supplier of secure text messaging services to the NHS and other Government bodies, and stores your information securely according to GDPR.

Because the study is part of a PhD research project, academic assessors may look at your data to check the accuracy of the study. You will remain anonymous to them during this process. They will only access your contact details if they need to contact you regarding the study.

The study's Trial Steering Committee will consider information about you in pseudonymised form in the event of any harm to you arising during the course of the study. You will remain

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anonymous to them. Any contact with you will be done via the researcher, who will also share any information regarding harm with your care team.

If you have given us permission to interview you about your experience of having AF or your experience of study participation, we will record the interview, and we will make notes on the interview. We may quote you directly in any study report, publication or presentation. We will take great care not to include in the quotes any information that could identify you directly.

Data protection

The University of York is the sponsor for this study based in the United Kingdom. The University will be using information given by you, and from your medical records, in order to undertake this study, and will act as the Data Controller for this study. This means that the University is responsible for looking after your information and using it properly. The University will securely store your personal information, including your name and contact details, for 10 years after the study has finished. At the end of this time, the information will be securely destroyed.

Our legal basis for processing your health information is Condition (j) in Article 9 (2) of the General Data Protection Regulations and your consent, as given by you in the Consent Form.

Your consent

By signing the Consent Form, you give permission for your data to be stored and used as described above. A copy of your signed Consent Form will be stored securely. You will be given a copy to keep.

Who is doing the research?

This study is being carried out by Karen Charlesworth, who is a PhD student at the University of York and the Research Director of the Northern College of Acupuncture, York. The PhD is overseen by the University of York's Health Sciences department under the supervision of Dr Judith Watson, Senior Research Fellow, and Professor David Torgerson, Head of the York Trials Unit. The Thesis Advisory Panel includes Ms Ada Keding, and is chaired by Professor of Cardiovascular Health Patrick Doherty; it formerly also included the late Emeritus Professor of Acupuncture Research, Hugh MacPherson.

The study's Trial Steering Committee is chaired by Ms Harriet Lansdown and comprises an expert acupuncturist member (Mr John Wheeler), an expert nutritional therapist member (Dr Sonia Williams), and a consultant cardiologist (Dr Sanjay Gupta).

The study is funded by the British Acupuncture Council and the Northern College of Acupuncture, York.

Who has reviewed and approved this study?

This study has been reviewed and approved by the University of York Health Sciences Research Governance Committee (ref: HSRGC/2019/346/H) and the UK Health Research Authority (HRA) and Health and Care Research Wales (HCRW) (ref. 20/LO/0598).

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Your rights

In this study, your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate.

If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum possible personally identifiable data.

If you lose the capacity to consent whilst you are taking part in the study, we will withdraw you from the study. We will keep the information about you that we have already obtained, but no further data will be collected and no further research procedures will be carried out.

If you are not happy with the study and want to complain, please contact the Head of the Trial Steering Committee, Harriet Lansdown. You can telephone on 01904 343305 or email on **tsc@sante-af.org**.

What if there is a problem?

If you have any concerns about any unexpected reaction to your acupuncture or nutritional therapy treatment during the study, please contact your acupuncturist or nutritional therapist.

If you have any medical problems or concerns relating to your AF, please contact your care team. In the event of requiring urgent care, you should contact the usual emergency services.

While we anticipate no harm or distress to anyone as a result of this study, it is important to state that there are no special compensation arrangements. In the unlikely event that you suffer injury or illness as a result of participating in this study, indemnity cover will be provided by the individual practitioners, the University of York and your GP practice.

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, please get in touch with the Head of the Trial Steering Committee, Harriet Lansdown, via the Northern College of Acupuncture. You can telephone on 01904 343305 or email on **tsc@sante-af.org**.

What do I do now?

If you have any questions, please get in touch with us, using the details at the end of this form. Alternatively, we will call you in the next few days to see if you have any questions.

If you don't have any questions and you DO want to take part in the study, please fill in ONE copy of the enclosed Consent Form and return it to it to us in the envelope provided. Once you have returned your completed Consent Form, we will contact you by phone again to check that you are eligible to take part in the study. If you are eligible, we will invite you to do an online baseline assessment at a date and time to suit you. After this assessment, we will enrol you in the study. For more information about how the study will progress, please see the Study Roadmap on page 20-21.

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If you do NOT want to take part in the study, you do not need to do anything further. We will not contact you without your permission. If you would like to tell us why you do not wish to take part, we would be very grateful, because this information is very helpful in designing a better study for the future. Please be aware that **you do not have to do this**. There is space on the enclosed Consent Form for you to tell us this, if you wish. You do not need to give us your name or contact details, or any other kind of information; you will remain completely anonymous. You can return this to us in the envelope provided. We thank you, and will not contact you again.

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Thank you for reading.

The following pages are for information only.

You do not have to read them, but they may provide helpful additional information.

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Santé-AF Sessions of Acupuncture and Nutritional Therapy Evaluation for Atrial Fibrillation

Feasibility study to inform a randomised controlled trial

Guide to Online Assessments

To reduce the risk of COVID-19, we are carrying out all the study assessments for Santé-AF online. This means that we will use Microsoft Teams video-calling software to guide you through the online study assessment. This section aims to answer your questions about this process.

We aim to make this as easy and unstressful as possible for you.

Please ask if you have any further questions (contact details are on the back page).

How many online assessments do I need to do for the Santé-AF study?

There are two online assessments in the Santé-AF study. The first is at the start of the study, and the second is about three months afterwards. Each assessment will take around 40 minutes. We will do this with you online.

In addition (if you have told us you're willing to be interviewed and you've been randomly selected for interview) we'll carry out your interview during the online assessment. It will take another 40 minutes.

How will I know what to do?

The Santé-AF researcher, Karen Charlesworth, will be online with you throughout your assessments. She will guide you through every part of it, and answer any questions you have.

Who will carry out my online assessments?

The Santé-AF researcher, Karen Charlesworth, will carry out your online assessments. Nobody else will be present or watching the assessment. Karen is a qualified acupuncturist, and is fully trained in carrying out medical assessments.

Will my online assessments be recorded?

If you've been selected for interview, we will record ONLY the interview. No other part of your online assessment will be recorded, although we will write down your measurements and the information you give us.

Participant Information Sheet: p17/22

What technology do I need to do the online study assessments?

We aim to take the stress out of using technology for the study assessments. If using technology is stressful for you, please let us know and we will do everything we can to make this as easy and stress-free as possible.

If you would prefer to use your own device, you will need EITHER:

- **a tablet (such as an Apple iPad or a Samsung Galaxy) with a microphone, speakers and a camera**. Most tablets are equipped with these;

OR

- **a smartphone (such as an Apple iPhone or a Samsung Galaxy) with a microphone, speakers and a camera**. All smartphones are equipped with these;

OR

- **a computer with a microphone, speakers and a camera**. Some computers are NOT equipped with these. We will check this with you during your screening phonecall (see the section **If I am eligible, what will happen next?** on page 3 for more information about the screening phonecall).

If you don't have a device of your own, or if you prefer not to use it, we will lend you the study's iPad for the online assessments. If you aren't familiar with iPads, the researcher will guide you through every step of the process.

You will need to connect the iPad to your home broadband, so please have your broadband name and password handy. The researcher will talk you through the connection process.

What software do I need to do the online assessments?

We will carry out the online assessments using the Microsoft Teams video-calling software. Teams is free to use on all kinds of device. It can be downloaded from the following location: https://teams.microsoft.com/uswe-01/downloads.

If you are using your own device and you don't have Microsoft Teams installed on your device, please go ahead and install this if you feel confident to do so. We'll do a quick test call with you to check everything is working ready for your assessment (see **How will I know it's all working?**).

If you don't have Microsoft Teams installed on your device, we'll lend you the study's iPad to carry out your online assessments. The software is all set up ready for you on the iPad.

We'll check all this with you during your screening phone call (see the section **If I am eligible, what will happen next?** on page 3 for more information about the screening phonecall).

How will I know it's all working?

If you're using your own device, we'll do a test call with you to check everything's working OK. When the researcher calls to carry out the screening phonecall, she will either do the test call with you then if you prefer, or she will agree a different date/time to suit you.

If you're using the study iPad, all you need to do is connect it to your home broadband and it should work without any problems. The researcher will talk you through the connection process. We'll deliver it to you just before your online assessment, and collect it again shortly afterwards, along with the other study equipment (see **Will I need any other equipment to do the online assessment?**).

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Will I need any other equipment to do the online assessment?

You'll need some other equipment to take measurements. We'll deliver these to your home just before your online assessment, and we'll collect them again shortly afterwards. The equipment we'll deliver is:

1. Weighing scales;
2. A blood pressure monitor;
3. A tape measure to take your waist and hip measurements.

Even though you may have this equipment yourself, it's important to the study that we use the same equipment for everyone. Every piece of equipment is thoroughly cleaned before and after each use, to minimise the risk of COVID-19.

Things that you will need to provide yourself include:

- **A pen** to fill in the questionnaire;
- **Your reading glasses**, if you use these;
- You might like to have **bathrobe or towel** nearby, to keep you warm and preserve your modesty during the parts of the assessment where you're in your underclothes.

Where should I do my online assessments?

It's important to do your online assessments in a room where you can be quiet and private.

The room will need a table and chair. This is because you'll need to rest your left arm on the table to take your blood pressure. We'll also ask you to keep your device (or the study iPad if you're using that) on the table in front of you during your assessment. When you take a measurement, we will ask you to show the results to us on-screen, so we can check it and record it accurately.

Part of the online assessment involves removing some clothing (so that you are only wearing your underwear when you weigh yourself, for instance). You can turn the camera off for these parts of the assessment if you prefer. You might want to keep a bathrobe or a towel handy, so you can keep warm.

What do I have to do in the online assessments?

These are the things we will do in the online assessments:

1. **Your medications.** The researcher will ask you about your current medications. If you like, you can simply collect your bottles/boxes and show them to the camera. The researcher will write down the names and dosages.
2. **AF symptom diary.** We will give you a copy of an AF symptom diary, which the researcher will ask you to keep with you and complete over the next 7 days. She will explain how to use it, and what to do when you've completed it.
3. **Your height.** The researcher will ask you your height.
4. **Questionnaire.** The researcher will ask you to fill in a questionnaire about your general health and your AF symptoms. If you prefer, she will stay online with you while you do this.
5. **Interview.** The researcher will interview you, if you have told us you're willing to be interviewed and you've been selected for interview.

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6. **Your blood pressure.** The researcher will guide you to take your blood pressure. To do this, you'll roll up your left sleeve right to the very top of your arm (you might need to slip your arm out of your sleeve to do this). Then you'll slide the cuff onto your left arm and push it up to the top of your arm. You'll tighten the cuff and turn the machine on. The machine will take 3 readings at 15-second intervals – you will need to sit still while it does this. At the end of this time, the researcher will take details of the reading for the study.
7. **Your weight.** The researcher will guide you to weigh yourself. The researcher will ask you to do this twice or three times, to check for accuracy. For this part of the assessment you'll need to take your shoes off and undress down to your underclothes. You can turn the camera off for this part if you like.
8. **Your waist and hip measurement.** The researcher will guide you to measure your waist and hips. She'll do this while you're in your underclothes, so that your clothing doesn't add any extra to the measurements. You can turn the camera off for this part if you like, although the researcher will ask you to turn the camera on briefly to check that you've positioned the tape measure correctly.
9. **CardioSTAT® heart monitor.** If you've been randomly selected to wear a CardioSTAT® heart monitor for 7 days after each assessment, the researcher will guide you to fit this. The CardioSTAT® is fitted centrally on your chest, just at the top of the breastbone, so female participants might want to keep a bathrobe or towel handy. The researcher will also explain what to do once the 7 days' monitoring are over.
10. **Returning the study equipment.** Finally, you'll collect up all the study equipment and put it back in the cases they came in, along with your completed questionnaire. The researcher will collect these from you shortly after your assessment ends, and the equipment will be thoroughly cleaned, ready for the next participant's online assessment.

I still have questions about online assessments. Who can I talk to?

If you still have questions, the study researcher, Karen Charlesworth, can answer these. She will call you in the next few days. But if you prefer to call the researcher, you can do this on either 01904 343305, or 07544 665882. If you would prefer to email, you can email her on karen.charlesworth@sante-af.org.

If you would like to ask any questions about this study, or about online assessments, please contact:

Karen Charlesworth, Santé-AF Researcher

Northern College of Acupuncture, 61 Micklegate, York YO1 6LJ

Telephone 01904 343305 or 07544 665882

Email karen.charlesworth@sante-af.org

Thank you for taking the time to read this Guide to Online Assessments.

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Santé-AF Sessions of Acupuncture and Nutritional Therapy Evaluation for Atrial Fibrillation
Feasibility study to inform a randomised controlled trial

Study roadmap

This roadmap gives an outline of the stages in the Santé-AF study. It is only for illustration, and timescales are approximate. An individual pathway may not follow this exact course.

Recruitment phase

1 Permission to Approach pack sent by your GP surgery
Example date: 1st March

You have already completed the Permission to Approach form and returned it to us in the envelope provided.

2 Full information pack sent to you
WHEN: Typically within 5 working days of us receiving your completed Permission to Approach form. Example date: 5th March

The full information pack contains:

- an introductory letter and reply-paid envelope;
- this Participant Information booklet, giving full information about the study;
- a Consent Form (two copies).

3 Phonecall from the researchers
WHEN: Typically within 2 working days of you receiving the full information pack. Example date: 7th March

We will call you to see if you have any questions about the study.

4 Return one copy of the Consent Form to us
WHEN: Typically within 3 weeks of the phonecall. Example date: 21st March

If you want to take part, complete one copy of the Consent Form and return it to us. You should do this within 3 weeks of the phonecall to make sure you are in time to join the study.

Enrolment phase

5 Screening phonecall from the researchers
WHEN: Typically within 5 working days of us receiving your signed Consent Form. Example date: 25th March

We will call you for a 20 minute conversation to work out whether you are eligible to take part. We'll also make arrangements to deliver the equipment for your online assessments.

6 Eligibility letter sent to you
WHEN: Typically within 3 working days of the screening phonecall. Example date: 28th March

We will send you a letter to confirm your full eligibility to take part in the study.

7 Baseline assessment
WHEN: Typically within 5 working days of you receiving the eligibility letter. Example date: 5th April

We'll guide you through an online study assessment. (Please see **A Guide to Online Assessments** on page 16-19 for more information about this). After the assessment you'll spend 7 days completing an AF symptom diary, and wearing the CardioSTAT® heart monitor if you have been selected to wear one. Please send these back quickly after the 7 days are up.

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Enrolment phase

Trial phase

8 Group placement letter sent to you

WHEN: Typically within 12 days of your baseline assessment.
Example date: 15th April

After we have all the data from your baseline assessment we'll write to you again to let you know what group you've been placed into. The groups are: Acupuncture plus Usual Care; Nutritional Therapy plus Usual Care; Usual Care only. If you're in the Acupuncture or Nutritional Therapy groups, we'll include details of your allocated practitioner, and you'll be invited to contact them to make your first appointment.

9 SMS (text) poll sent to you

WHEN: Typically within 2 days of the group placement letter.
Example date: 16th April

We will send two SMS messages (texts) to your mobile phone. The first will ask you to rate your level of satisfaction with the group you've been allocated to. The second will ask whether you expect your AF to improve, stay the same, or get worse during the study.

10 Treatment period

WHEN: Typically the 8-10 weeks after receiving the group placement letter.
Example dates: 20th April – 30th June

During this time you'll be EITHER:

- receiving Acupuncture or Nutritional Therapy along with your usual NHS treatment for your atrial fibrillation (if you're in the Acupuncture or Nutritional Therapy groups)

OR

- receiving your usual NHS treatment for your atrial fibrillation only (if you're in the Usual Care group).

During this period we'll pay you a travel subsidy of £5 per appointment if you're in the Acupuncture group. Towards the end of this period we'll also contact you to arrange a time for your second (final) online assessment.

11 Three-month assessment

WHEN: Typically within 12 weeks of receiving the group placement letter.
Example date: 15th July

We'll guide you through an online study assessment. (Please see **A Guide to Online Assessments** on page 16-19 for more information). After the assessment you'll spend 7 days completing an AF symptom diary, and wearing the CardioSTAT® heart monitor if you have been selected to wear one. Please send these back quickly after the 7 days are up. Once we've received your symptom diary and the data from the CardioSTAT® monitor if you're wearing one, we'll send you a £10 retail voucher as a thank-you for your time.

12 End of study

WHEN: After the end-of-intervention assessment.
Example date: 15th July

Once you have completed the end-of-intervention assessment, you have finished the study. We'll send you a complimentary copy of the study results when these are available (currently anticipated in the autumn of 2022). **Thank you for your time!**

If you have any questions about the study, please contact the Santé-AF researcher, Karen Charlesworth, on 01904 343305 or 07544 665882, or by email on karen.charlesworth@sante-af.org.

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Santé-AF Sessions of Acupuncture and Nutritional Therapy Evaluation for Atrial Fibrillation

Feasibility study to inform a randomised controlled trial

Northern College of Acupuncture, 61 Micklegate, York YO1 6LJ
Telephone 01904 343305 or 07544 665882
Email karen.charlesworth@sante-af.org

How to contact us

If you would like to ask any questions about this study, please contact:

Karen Charlesworth, Santé-AF Researcher
Northern College of Acupuncture, 61 Micklegate, York YO1 6LJ
Telephone 01904 343305 or 07544 665882
Email karen.charlesworth@sante-af.org

If you have concerns about the study or wish to make a complaint, please get in touch with the Head of the Trial Steering Committee:

Harriet Lansdown, Head of the Trial Steering Committee
Northern College of Acupuncture, 61 Micklegate, York YO1 6LJ
Telephone 01904 343305
Email tsc@sante-af.org

Thank you for taking the time to read this information booklet.
If you decide to take part, please keep this leaflet for future reference.

University of York | nca Northern College of Acupuncture

HRA/HCRW & NHS REC ref: 20/LO/0598 | IRAS Project ID: 268585 | ISRCTN13671984

Consent form: p1/4

Santé-AF Sessions of Acupuncture and Nutritional Therapy Evaluation for Atrial Fibrillation
Feasibility study to inform a randomised controlled trial

Study ID no

Participant Consent Form

Version 1.3 – Date 26th January 2021

If you wish to take part in the Santé-AF study, please put your initials in all of the boxes below, then sign and date this form.
If you wish to take part, ALL boxes must be initialled to indicate agreement.

If you DO NOT wish to take part, please go to page 4 to tell us this.

Section 1: Your informed consent

	Please initial all boxes	
1.	your initials	I confirm that I have read and understand the Participant Information Sheet version 1.4 dated 26th January 2021 for the above study. I have been offered the opportunity to ask any questions about the study, which have been answered to my satisfaction.
2.	your initials	I am willing to receive a telephone call to find out whether I am fully eligible to take part in the study.
3.	your initials	I understand that any information I give will not shared in identifiable form with anyone outside the study, in accordance with GDPR and the Data Protection Act (2018). I understand that my information will be securely stored for 10 years after the end of the study, and that it will be analysed in anonymised and pseudonymised form as part of the study data, including possible publication. I understand that I will not be identifiable in any analysis or publication.
4.	your initials	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, and without my medical care, legal rights or standard treatment provided to me by the NHS being affected in any way.
5.	your initials	I am willing to receive EITHER acupuncture plus my usual care, OR nutritional therapy plus my usual care, OR my usual care only, for the purposes of this study.
6.	your initials	If I am randomly assigned to receive acupuncture, I am willing to travel to acupuncture appointments and to comply with the COVID-19 safety requirements of the acupuncturist I am treated by.
7.	your initials	If I am randomly assigned to receive Nutritional Therapy, I am willing to attend online appointments.
8.	your initials	I am willing to carry out two online Study Assessments over the course of approximately three months, whatever group I am placed in.
9.	your initials	I confirm that EITHER I have a device equipped with video-calling software OR I am happy to use the study's iPad (under the guidance of the researcher) to conduct online assessments.
10.	your initials	I confirm that I have a home broadband connection covering a quiet, private room in my home where I am willing to carry out the online study assessments.
11.	your initials	I am the owner of, and able to use, a mobile phone whose number I will share with the researchers for the purposes ONLY of receiving telephone calls and SMS texts about the Santé-AF study in relation to study appointments and data collection. I agree to the processing of my contact details, including my name and mobile phone number, through an NHS-approved third-party communications supplier. This will not be shared with any other party in any way whatsoever.

HRA/HCRW & NHS REC ref: 20/LO/0598 | IRAS Project ID: 268585 | ISRCTN13671984

University of York

nca Northern College of Acupuncture

Consent form: p2/4

12. your initials — I have a current email address that I will share with the researchers for the purposes of receiving emails about the Santé-AF study in relation to study appointments and data collection. This will not be shared with any other party in any way whatsoever.

13. your initials — I give permission for my GP to be informed about my participation in the Santé-AF study.

14. your initials — I understand that, if I disclose information that (in the professional judgement of the researcher or my practitioner) suggests I may represent a danger to myself or others, that the practitioner or the researcher will inform my GP as part of a duty of care.

15. your initials — I understand that there are no special compensation arrangements for this study. I understand that in the unlikely event that I suffer injury or illness as a result of participating in the Santé-AF study, indemnity cover will be provided by the individual practitioners, the University of York and my GP practice.

16. your initials — If I am selected to wear a CardioSTAT® heart monitor, I am willing to fit this myself with guidance, wear the monitor for 7 days, and to return it to Icentia Limited in the envelope provided for processing. I am willing to do this twice during the study. I understand that the data will be processed by Icentia Limited and shared with the researcher, my GP, and the study's consultant cardiologist. I agree to the processing and sharing of my data in this way. *I understand that I may or may not be selected to wear a heart monitor*.

17. your initials — I confirm that I am not currently taking part in any other medical research that would prevent me taking part in the Santé-AF study, or prevent me attending assessment appointments. I will make the researchers and/or my practitioner aware of any other research involvement beginning **after** I am recruited to the Santé-AF study. I understand that if I do not do this, the study researchers and practitioners are not liable for any effect that my participation in other research may have in conjunction with my participation in the Santé-AF study. I understand that if I choose to take part in other medical research that, in the opinion of the researchers, would make my continued participation in the Santé-AF study inadvisable, I may be asked to leave the study. In such a case, data already collected with consent would be retained and used in the study. No further data would be collected.

18. your initials — I understand that (if I am placed into a group to receive acupuncture or nutritional therapy) some of the information from my treatments/consultations with my practitioner will be shared in pseudonymised form with the study's researcher. This will be details of treatments given or advised, not my personal information. I give permission for this information to be shared pseudonymously.

19. your initials — I understand that health information I give to my practitioner during treatments/consultations, or to the study researcher during assessments, will be shared with the study's consultant cardiologist and/or my GP if, in the opinion of Icentia Limited, my practitioner or the researcher, it warrants further investigation. I give permission for my GP to be contacted in these circumstances.

20. your initials — I understand that data collected from me during the course of the study is not being collected for the purposes of my medical care, but for research purposes, and that I remain responsible for seeking my own medical care for any symptom I experience that is of concern to me.

21. your initials — I agree to the University of York holding copies of my consent form, other study-related documents and my contact details to allow them to demonstrate my consent, send me notifications and information, and to assist with study data collection. I understand that this data will be stored for 10 years from the date of study completion, in accordance with the University's data retention schedule for postgraduate research.

22. your initials — I understand that the information collected from me may be used to support other research in the future, and may be shared in pseudonymised form with other researchers.

23. your initials — I confirm that I am able to give my informed consent using this form. In the event that I lose the ability to consent during the study, I understand that I will be withdrawn from the study but that data already collected with consent would be retained and used in the study. No further data would be collected.

24. your initials — I confirm that I am not shielding, clinically vulnerable or clinically extremely vulnerable with regard to COVID-19, and I am not living with anyone who falls into any of these categories.

25. your initials — **I agree to take part in the Santé-AF study.**

Please continue to Section 2 on the next page

Consent form: p3/4

Section 2: Optional involvement

Please do not complete this section if you do not wish to take part in the study at all. Instead, to tell us that you do not wish to take part at all, please go to page 4.

In addition to the statements on Page 1 and 2, **please initial the following boxes to indicate whether you agree with the following statements**. These are optional. Your participation in this study will not be affected if you say no to these statements.

	Yes	No
I am willing to be interviewed twice (at the start, and about 3 months after the start) about my experience of having AF and of taking part in the Santé-AF study. I agree to any academic assessors having access to my interview data, which will be pseudonymised so my identity remains unknown to them. *I understand that I may or may not be interviewed.*	your initials	your initials
If I take part in an interview, **I am willing for it to be recorded, and for notes to be kept on the interview.** I understand that pseudonymised written quotations from the interview may be used in publications and presentations. I understand that I will not be identifiable in these quotations.	your initials	your initials
I understand that findings from the Santé-AF feasibility study will relate to the feasibility of a future larger-scale trial. I would like to receive a copy of the findings at study close (expected 2022).	your initials	your initials

Section 3: Signature and date

Please do not complete this section if you do not wish to take part in the study at all. Instead, to tell us that you do not wish to take part at all, please go to page 4.

Print name

Name of participant *(please print)*

Signature

Signature of participant *(please sign your name)*

D D M M Y Y Y Y

Date

Please return ONE COPY of this Consent Form to the Northern College of Acupuncture in the envelope supplied. The other copy is for you to keep for your records. We will also send you a copy of your signed consent form.

University of York | nca Northern College of Acupuncture

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Consent form: p4/4

SID

Section 4: If you do NOT want to take part

If you do NOT want to take part in the Santé-AF study, please put a TICK in this box: please tick

We would be very grateful if you could tell us briefly why you do not want to take part in the study. **You do not have to do this**, but if you do, it will help us to design a better study in future. Please write here:

Thank you. Please return this form to the Northern College of Acupuncture in the envelope provided. We will not contact you again.

Northern College of Acupuncture, 61 Micklegate, York YO1 6LJ

UNIVERSITY of York

nca Northern College of Acupuncture

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Appendix C: Study assessment material

Assessment material was too large to include as an Appendix. Instead, it has been uploaded to the online repository Open Science Framework, where it can be viewed and downloaded.

Screening call questionnaire (6pp): **https://osf.io/6brcs**

Baseline interview topic guide (3pp): **https://osf.io/m85se**

Baseline questionnaire (24pp): **https://osf.io/9cq2r**

Follow-up interview topic guide, Acupuncture group (4pp): **https://osf.io/pfxur**

Follow-up interview topic guide, NT group (4pp): **https://osf.io/mn6ve**

Follow-up interview topic guide, Usual Care group (3pp): **https://osf.io/gu6qs**

Follow-up questionnaire (24pp): **https://osf.io/d2j59**

Symptom diary (4pp): **https://osf.io/rvg8z**

Measurements and medications log (Excel file): **https://osf.io/3sq4z**

Information on the CardioSTAT® ECG monitor for participants: **https://osf.io/mxvhz**

Assessment timings log (Excel file): **https://osf.io/zsthg**

Appendix D: Analyses not included in this thesis

This Appendix includes two analyses set out in the study protocol which were judged not of use to a future trial and were therefore not included in the final thesis. They are reported here for completeness.

Objective 2b: Similarity of participant characteristics to other AF studies

Analysis of this domain was carried out, but was thought to be of little use to a future trial in the context of other changes recommended to eligibility criteria.

To check whether the baseline characteristics of the Santé-AF cohort were similar to that of trials of other interventions for AF, the key characteristics were compared with two recent AF research cohorts:

- The CABANA trial (Packer et al., 2019), a 126-centre trial across 10 countries randomising 2,204 patients to either catheter ablation or rhythm/rate control medication;
- The study of trends in AF carried out by Lane et al. (2017) using data from the Clinical Practice Research Datalink (CPRD), a UK primary care database.

Table 39 shows the comparison of key participant characteristics with those of participants in CABANA and CPRD. It also shows the percentage difference (both positive and negative) between each study in comparison with Santé-AF, to support the determination of feasibility for this Objective.

Of 10 Santé-AF participant characteristics compared with the CABANA trial, eight showed more than 20% difference. These included race, where Cabana had attracted 3.5% Black and 4.4% Other races participants, each 100% more than Santé-AF; presence of the comorbidities hypertension, diabetes, prior CVA/TIA and sleep apnoea (an average of 42.3% difference); and sex (Santé-AF attracted 75.9% male participants compared with CABANA's 62.8%, a difference of 20.9%). The median age of the participants showed a 10.3% difference, with the median Santé-AF age being 61 compared with the CABANA median of 68.

Of seven Santé-AF characteristics compared with the UK CPRD registry study, six showed more than 20% difference. Notable differences included the proportion of participants with the comorbidities hypertension and prior CVA/TIA (31.5% and 52.7% lower respectively in Santé-AF) and diabetes (21.1% higher in Santé-AF); and the number of participants taking beta-blocker and/or ACE inhibitor medications (208.1% higher and 29.8% lower in Santé-AF respectively). The disproportionate number of men to women compared unfavourably with the almost equal proportions of each in the CPRD study, due to the latter being a registry study rather than a trial.

The average age of participants in the CPRD study was 74.2 years, a difference of 18.7% from Santé-AF's 60.3 years.

Table 39: Similarity of participant characteristics to other AF studies

	Santé-AF	CABANA (Packer et al., 2019)	CABANA % difference from Santé-AF	CPRD (Lane et al., 2017)	CPRD % difference from Santé-AF
Participants, n	29	2 204	–	57 818	–
Age, y	61 (56.5–65) 60.3±6.25	68 (62–72)	10.3%	74.2±11.7	18.7%
Sex					
Male	22 (75.9)	1 385 (62.8)	-20.9%	29 875 (51.7)	-46.8%
Female	7 (24.1)	819 (37.2)	35.2%	27 943 (48.3)	50.1%
Time since AF onset, y	2.7 (1.9–5.0)	1.1 (0.3–4.3)	-145.5%	–	–
Race					
Asian	0	–	–	–	–
Black	0	77 (3.5)	100.0%	–	–
White	29 (100)	2 025 (91.8)	-8.9%	–	–
Other	0	98 (4.4)	100.0%	–	–
BMI	29.9 (26.9–33.8) 30.3±5.4	30 (26.5–34.5)	0.3%	–	–
Comorbidities					
Hypertension	11 (37.9)	1 776 (80.5)	52.9%	31 962 (55.3)	31.5%
Diabetes	4 (13.8)	561 (25.5)	45.9%	6 595 (11.4)	-21.1%
Prior CVA or TIA	2 (6.9)	220 (9.9)	30.3%	8 440 (14.6)	52.7%
Sleep apnoea	4 (13.8)	508 (23.0)	40.0%	–	–
Medication					
Beta-blocker	21 (72.4)	–	–	13 592 (23.5)	-208.1%
ACE inhibitor	5 (17.2)	–	–	14 141 (24.5)	29.8%
Aggregate % difference			49.2±42.3		57.4±58.3

Figures shown as median (Q1–Q3), or μ±SD for continuous data, or n (%) for binary data
Figures in grey cells are comparisons with Santé-AF. Darker grey cells show ≥20% difference

Objective 3c: Number of compliance prompts needed

Analysis of this domain was carried out, but was not judged to be useful for a future trial on the basis that a future trial will use its own methods of prompting.

This domain was intended to gather information regarding the extent of prompting required for participants to return symptom diaries and CardioSTAT® ECG monitors, where applicable; and also to remind participants to respond to the post-randomisation SMS poll requesting levels of satisfaction with group allocation and their expectation of treatment. Compliance prompts were sent by SMS message.

Table 40 shows the number of compliance prompts sent for each purpose, and the data returned in response to each prompt.

Table 40: Compliance prompts and volume of data elicited by each

Prompt for	First prompt to n p'pts (%)	% data returned	Second prompt to n p'pts (%)	Cumulative % data returned	Third prompt to n p'pts (%)	Cumulative % data returned
Post-randomisation SMS poll response	6 (20.6)	50%	3 (10.3)	67%	1 (3.5)	67.0%
Baseline Symptom Diary	2 (6.9)	100%	–	–	–	–
Baseline CardioSTAT®	1 (3.5)	100%	–	–	–	–
Follow-up Symptom Diary	3 (10.3)	67%	1 (3.5)	100%	–	–
Follow-up CardioSTAT®	1 (3.5)	0%	1 (3.5)	100%	–	–

Appendix E: Systematic review material

A range of supplementary material for this thesis is included below. Each document has been uploaded to the online repository Open Science Framework, where it can be viewed and downloaded.

1. Brief definitions of each complementary therapy included in the systematic review: **https://osf.io/58gza**
2. Search logs for bibliographic databases (updated November 2023) with search strings/adaptations to each source searched (Excel file): **https://osf.io/gr7y8**
3. Identified sources investigated for operational status, accessibility and relevance in March 2023 (updated November 2023): **https://osf.io/u43ac**
4. Reviews and extracted studies (updated November 2023): **https://osf.io/6en4y**
5. Search log, all other sources (updated November 2023) (Excel file): **https://osf.io/5n4rh**
6. Cochrane Risk of Bias 2 assessments for included studies: **https://osf.io/w4j5q**
7. Emails sent to corresponding authors: **https://osf.io/tcus5**
8. Characteristics of excluded studies: **https://osf.io/zcjd9**

Abbreviations

AF	Atrial fibrillation
AFEQT	Atrial Fibrillation Effect on QualiTy of life questionnaire
AR	Adverse reaction
BAAB	British Acupuncture Accreditation Board
BAcC	British Acupuncture Council
BANT	British Association for Nutrition and Lifestyle Medicine
BMI	Body mass index
BP	Blood pressure
CHSRI	Cochrane Handbook for Systematic Reviews of Interventions
CI	Confidence interval
CID	Clinically important difference
CNHC	Complementary and Natural Healthcare Council
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CPD	Continuing professional development
CRN	Clinical Research Network
DASH	Dietary Approaches to Stop Hypertension
DOAC	Direct-acting oral anti-coagulant (also known as NOAC, or Novel…)
ECG	Electrocardiogram
EOI	Expression of interest
EOT	End of treatment
EQ-5D(-5L)	EuroQoL quality of life questionnaire
ESC	European Society of Cardiology
ETCs	Excess Treatment Costs
EU	European Union
FODMAP	Elimination diet focused on Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols

GCP	Good Clinical Practice (research training)
GDPR	General Data Protection Regulation
GP	General practitioner (primary care)
HCRU	Healthcare resource utilisation
HR	Hazard ratio
HRA	(NHS) Health Research Authority
HRQoL	Health-related quality of life
HSRGC	Health Sciences Research Governance Committee (University of York departmental ethics body)
ICHOM	International Consortium for Health Outcomes Measurement
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number (clinical trials registry)
ITG	Interview Topic Guide
ITT	Intention-to-treat analysis
MA	Meta-analysis
MCID	Minimum clinically important difference
MID	Minimum important difference
MM	Mixed methods
MRC	Medical Research Council
NCA	Northern College of Acupuncture
NHS	National Health Service (UK)
NIHR	National Institute for Health Research
NRPPS	Non-randomised pre-post study
NSR	Normal sinus rhythm
NT	Nutritional therapy / Nutritional therapist
NTEC	Nutritional Therapy Education Commission
ONS	Office for National Statistics
OR	Odds ratio

OSA	Obstructive sleep apnoea
PE	Process evaluation
PHE	Public Health England
PIC	Participant Identification Centre (GP practice)
PICO(S)	Population, Intervention, Comparator, Outcome, (Study type)
PICT	Preference-informed complementary trial
PIS	Participant Information Sheet
POR	Patient-oriented research
PPI	Patient and public involvement
PRECIS-2	Pragmatic-explanatory continuum indicator summary
PRO(M)	Patient-reported outcome (measure)
PSA	Professional Standards Authority
PtA	Permission to approach
QoL	Quality of life
RCT	Randomised controlled trial
R&D	Research & Development (hospital department overseeing research)
REC	Research ethics committee
RFM	Risk factor management
RR	Risk ratio / relative risk
RTA	Reflexive thematic analysis
SD	Standard deviation
SES	Socioeconomic status
SID	Study ID number (for participants)
SIV	Site initiation visit
SMART	Sequential Multiple Assignment Randomised Trial
SMS	Short messaging service (i.e., mobile phone text)
SoECAT	Schedule of Events Cost Attribution Template
SR	Systematic review
SSCs	Service Support Costs

TCM	Traditional Chinese Medicine (used in this study to indicate a style of acupuncture, but often used in the literature to indicate a therapy more accurately known as “Chinese herbal medicine”)
TENS	Transcutaneous Electrical Nerve Stimulation
TSC	Trial Steering Committee
UoY	University of York

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A

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