Thesis title: A novel evidence-based medicine approach for determining aetiology of side effects with statins.

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Statement of originality

This is to certify that this thesis, for consideration for PhD degree is the result of my own study and research and has been composed by myself and all the assistance received in preparing this thesis and sources has been acknowledged and seen by my supervisors before presentation.

Abstract

Statins are a proven highly effective way to prevent and manage cardiovascular disease. Adherence to cardiovascular prevention medication, including statins, is poor and results in morbidity, mortality and increased healthcare costs. Side effects are often a cause for stopping statins in clinical practice despite there being equivalent rates of side effects between statins and placebo tablets in randomised blinded control trials. The Self-Assessment Method for statin side effects Or Nocebo (SAMSON) developed a phone application to allow participants to test for themselves in a randomised controlled trial whether statins side effects were greater when taking a statin compared to a placebo and also compared tablet periods to no treatment periods. The results demonstrated there was no significant difference between statin or placebo months but there was a significant difference between tablets and no tablet months. What is more, after being given their personal trial results 50% of participants restarted a statin. The results offer a potential intervention to help patients restart statins which are a drug indicated for various disease conditions not just for cardiovascular disease. This type of intervention also has potential utility in other types of drug classes where nocebo is an issue. Furthermore, the research reflects on individual experiences of statins and finds that although there is trust in medical professionals there is a lot of counter-information about statins that can make patients unsure what information is accurate. This thesis raises an important questions about whether patients knowing about the nocebo effect might help them to be less likely to fall foul of it. In light of the findings of this thesis, current management of suspected side effects with statins might not be effective or even counterproductive and review of existing guidelines in light of the results of this thesis are recommended.

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Abbreviations

AE	Adverse Event
CASP	Critical Appraisal Skills Programme
GCP	Good Clinical Practice
HRA	Health Research Authority
ICTU	Imperial Clinical Trials Unit
IMPD	Investigational Medicinal Product Dossier
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare products Regulatory Agency
PIC	Patient Identifying Centre
PT	Preferred Term
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAMSON	Self-Assessment Method for Statin side-effects Or Nocebo (SAMSON)
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOC	System Organ Class

Publications arising

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1 Introduction

1.0 Chapter overview

Globally, cardiovascular disease (CVD) is a significant cause of mortality and morbidity. statins offer an effective means of CVD prevention. In primary and secondary prevention respectively, 47% and 41% of patients discontinue statins and only 72% and 75% of those who discontinue restart a statin (Vinogradova et al. 2016). Many people do not continue statins. This chapter will present evidence of their proven effectiveness and safety. The consequences of statin discontinuation are increased cardiovascular events, mortality and healthcare costs. Patients frequently stop statins due to side effects, commonly myalgia, yet evidence from clinical trials indicates that rates of adverse symptoms occur equivalently when a person is taking a placebo compared to a statin. This could indicate a psychological rather than a pharmacological component to some side effects. This calls into question current approaches to managing adverse symptoms with statins, because their aetiologies are not necessarily correctly understood. It also indicates there may be differences in adverse symptoms experienced in clinical trials compared with everyday practice.

This chapter will demonstrate the evidence that supports statins as an effective treatment for the prevention and management of CVD. It will demonstrate that adverse symptoms caused by the pharmacology of statins is overplayed. Factors associated with medicine non-persistence and non-adherence will be explored, focussing on statins. The nocebo effect will be examined as a possible explanation for non-persistence with statins in some patients. The n-of-1 trial design will be introduced as a possible solution at the individual level to investigate this issue with statins and the key objectives and hypotheses of this thesis will be set out. This chapter concludes by overviewing the structure of the subsequent chapters in this thesis.

1.1 Pathophysiology of cardiovascular disease

CVD is the leading cause of death worldwide (GBD 2013 Mortality and Causes of Death Collaborators 2015), accounting for 30% of all deaths of all ages (World Health Organisation 2012). In the UK, in 2012, 28% of deaths were caused by CVD (Bhatnagar et al. 2015). More than 915 000 people in the UK have had a myocardial infarction (MI) and more than 1.3 million live with angina.

The WHO defines CVD as disorders of the heart, vascular diseases of the brain and diseases of the blood vessels (Mendis 2011). These are subdivided into ‘atherosclerotic CVD’ and ‘non-atherosclerotic CVD’. Atherosclerosis is an underlying disease process of the blood vessels and leads to the build-up of plaques in the walls of the vessels, which can cause narrowing and thrombus that can block blood flow and lead to life threatening conditions if occlusions occur in the heart, brain, aorta or peripheral vascular system. ‘Non-atherosclerotic CVD’ include congenital heart disease, rheumatic heart disease, cardiomyopathies and cardiac arrhythmias.

Various factors accelerate atherosclerotic CVD, including hypertension (high blood pressure), smoking, high levels of low-density lipoprotein (LDL) cholesterol, diabetes mellitus, obesity and genetic predisposition (Hajar 2017). The pivotal role of high cholesterol is emphasised, by the premature mortality associated with patients with familial hypercholesterolemia (Mabuchi et al. 1989). High LDL cholesterol is a modifiable risk factor. Treatments that lower LDL cholesterol such as statins are very important in the prevention and management of cardiovascular disease.

1.2 Medical therapy for treatment and prevention of cardiovascular disease

Since the 1980s there has been a reduction in deaths from coronary heart disease with about half of this decrease being attributed to effective drug treatments (Ford et al. 2007). Randomised control trials provide strong evidence that drugs lowering LDL cholesterol reduce the incidence of ischaemic heart disease and stroke (Law et al. 2003, MacMahon et al. 1990, Collins et al. 1990, Law et al. 2003, PATS Collaborating Group 1995, PROGRESS Collaborative Group 2001, Antithrombotic Trialists’ Collaboration 2002).

Statins are a widely used drug to lower LDL cholesterol (Davies et al. 2016). Different statins reduce LDL cholesterol by differing amounts. In 58 trials, reducing LDL cholesterol by 1.0 mmol/l reduced risk of IHD by 11% in the first year of statin treatment and 33% after three to five years (Law et al. 2003).

Previous UK CVD prevention guidelines recommended focussing equally on patients with established CVD, those with diabetes and those at high risk (CVD

risk of >20% in 10 years) (British Cardiac Society et al. 2005) More recent risk calculators recommend considering life time risk (JBS3 Board 2014, Authors/Task Force Members: et al. 2012), CVD prevention therapy is also recommended for those with a family history of CVD or a particularly high single risk factor such as markedly high blood pressure, elevated total cholesterol or familial hypercholesterolemia.

Current guidelines support the use of statins in the secondary prevention of CVD. Statin therapy is the first choice for lipid lowering therapy. Statins lower the level of cholesterol in the blood by blocking the enzyme HMG-CoA-Reductase in the liver that produces cholesterol which leads to a reduction in cholesterol synthesis and lipid metabolism (Stancu and Sima 2001). Intensive use is recommended in patients who have had a previous MI. Statins are also recommended for patients after an ischaemic stroke. See Table 1 for the percentage reduction in LDL cholesterol by statin. There are currently five approved for use in the United Kingdom. In 2001, Cerivastatin was withdrawn from the pharmaceutical market because 31 patients died from acute renal failure due to rhabdomyolysis (Stancu and Sima, 2001). It was 10 times more myotoxic than other licensed statins (Stancu and Sima, 2001). Elimination half-lives for statins range from 1 hour for Fluvastatin to 19 hours for Rosuvastatin (Schachter 2005) and can take up to 2-months to reduce cholesterol and requires long-term use to continue to lower cholesterol.

*Table 1: Percentage reduction in low-density lipoprotein cholesterol by statin * MHRA there is an increased risk of myopathy with Simvastatin 80mg* (MHRA 2014).

	Daily dose (mg)				
Statin	**5**	**10**	**20**	**40**	**80**
Atorvastatin	31%	37%	43%	49%	55%
Fluvastatin	10%	15%	21%	27%	33%
Pravastatin	15%	20%	24%	29%	33%
Rosuvastatin	38%	43%	48%	53%	58%
Simvastatin	23%	27%	32%	37%	42%*

1.3 Patterns of statin prescribing and the global drug market

In 2014, in England, a total of 1.1 billion prescriptions were dispensed, of which statins were the most prescribed medicine; the 3 most commonly prescribed statins were: Simvastatin (37.8 million items), Atorvastatin (22.2 million items) and Pravastatin (3 million items) (Prescribing & Medicines Team 2015).

Between 2008-2011, lipid-lowering drug use was studied in 131,603 high-risk CVD patients. 6-months after a CVD event, 63.1% were receiving a statin and usually continued on the same statin at the same untitrated dose. In the first year, 69.3% were at the LDL-cholesterol goal <2.5mmol/l or were using a high-intensity statin dose (Nordstrom et al. 2015). Most prescribers were adhering to recommendations of prescribing a statin in established and high risk groups, but the longer term maintenance and dose of statin prescription was often less than recommended (Boggon et al. 2012). In the United States, between 2012 to 2013, 39.2 million individuals over the age of 40 years were taking a statin (Salami et al. 2017).

The global hyperlipidaemia drug market was valued at 19.3 billion United States dollars as of 2016 (Grand View Research 2018). Compound annual growth rate forecast up to 2022, is predicted to be 2.3%, largely due to redefinition of cardiovascular risk and novel drug classes. In 2016, statins still held the greatest market share of 30% compared to bile acid sequestrants, cholesterol absorption inhibitors, fatty acid derivatives, PCSK9 inhibitors, and miscellaneous anti-hyperlipidemic agents. Europe and North America hold the biggest overall market for hyperlipidaemia drugs (Grand View Research, 2018).

1.4 Issues with medication adherence and persistence with medical therapy

Despite effective therapies to prevent and treat CVD, non-persistence to recommended medications is a frequent barrier to CVD prevention and contributes to hundreds of thousands of deaths each year and higher healthcare costs (Kolandaivelu et al. 2014). Good persistence with statins is associated with decreased cardiovascular events, mortality and hospitalisation costs (Rosenson 2016, Mohammed et al. 2016, Collins et al. 2016, Banach et al. 2016, Burnier 2017, Mohan et al. 2019, Deshpande et al. 2017, Cheen et al. 2019, Albarqouni et al. 2017).

Following a MI only 66% of patients on the United States (US) PREMIER registry reported taking aspirin, β-blockers, and statins (Ho et al. 2006) this was echoed in the Ontario-based EFFECT register with only 78% of patients filling prescriptions 120 days post MI (Jackevicius et al. 2008) and only 72% for the CRUSADE and ACTION registries in the US (Melloni et al. 2009). Furthermore, evidence suggests that over time CVD medicine adherence (compliance) gets

worse (GBD 2013 Mortality and Causes of Death Collaborators 2015). A Scottish study, which followed for at least 1 year 73716 patients newly initiating statins (of which 14.4% were receiving statins for secondary prevention of CVD and 85.6% for primary prevention) showed only a 52.6% adherence to treatment (Rezende Macedo do Nascimento et al. 2020). In her study, patients prescribed higher intensity statin regimes showed better overall adherence. Rates of persistence are equivalently poor with anti-hypertensive and anti-platelet therapies (Brown and Bussell 2011).

Factors correlated with non-adherence include use of other therapies for chronic conditions, complex dosing schedules, high number of prescriptions, extremes of age, non-white race, depression, lower socioeconomic class, poor literacy, low education level and practitioner speciality (Cheen, Tan, Oh, et al., 2019; (van Dulmen et al. 2007, Avorn et al. 1998). Affordability of medication is a barrier particularly in low and lower-middle income countries (Yusuf et al. 2011) but adherence still remains a problem when cost is not an issue (Kardas et al. 2013). Population studies in Denmark and UK, showed negative stories in the national media were also associated with early discontinuation of statins (Nielsen and Nordestgaard 2016, Matthews et al. 2016).

A 2-year cohort study followed up statin initiation and showed only 40% of patients were still taking statin medication 2-years after an acute coronary syndrome but was lower still for primary prevention (Jackevicius et al. 2002).

Statins have a good safety profile (Newman et al. 2019) and are inexpensive (Banach, Stulc, Dent, et al., 2016). Collins argues that side effects caused by statins are exaggerated and the actual cases of myopathy or muscle related symptoms are rare and resolve rapidly when statins are stopped (Collins, Reith, Emberson, et al. 2016). Myopathy with statins is more likely if inhibitors of cytochrome P450 or other inhibitors of statin metabolism are administered alongside statins (Stancu & Sima, 2001). Finegold performed a meta-analysis of a series of 29 double blind randomised controlled trials comparing the effects of statins with placebo. They described the side effect reporting of 83,880 participants; there was no sign of a greater adverse symptom rate with statins compared to placebo but there was a small increase in new onset diabetes associated with statin treatment, with an excess absolute risk of 0.5% (95% CI 0.1-1%, $p = 0.012$) (Finegold et al. 2014). These findings were supported by a

review by Kashani (Kashani et al. 2006). A glycaemic effect of statins has been reported elsewhere (Rosenzweig et al. 1993) but the frequency of other types of statin side effects in placebo-controlled trials do not exceed that of placebo. In one study, adverse event rates for myalgia in a randomised controlled trial were equivalent between statin and placebo arms in the first phase of the trial, but in the second unblinded phase muscle related complaints were significantly higher in the group taking statins vs. the group not taking statins (Gupta et al. 2017).

More generally, an analysis of 231 high profile journal publications of randomised placebo-controlled clinical trials covering various medical domains, showed placebo associated adverse events (AEs) common for both subjective (e.g., pain) and objective conditions (e.g., hypoglycaemia). Frequency of AEs and serious adverse events (SAEs) in placebo recipients varied across medical domains, 19% of placebo recipients had 1 or more AE considered likely to be drug-related (Mahr et al. 2017).

Despite available evidence to suggest that the majority of adverse symptoms with statins are not pharmacological, the current management in clinical practice focusses on the assessment of pharmacological side effects and is exemplified by the statin intolerance pathway, see Figure 1. For example, in the United Kingdom, the National Institute for Health and Care Excellence (NICE) produce evidence-based guidance for the NHS and its practitioners. In the event of statin intolerance it is recommended stopping statins and restarting when symptoms resolves to check if symptoms are related to the statin (NICE 2015). NICE groups licensed statins by percentage reduction in LDL cholesterol low intensity (20-30%), medium intensity (31-40%) and high intensity (greater than 40%) (NICE 2016). In addition to retrying a statin, they also recommend reducing dose within the same intensity group and changing the statin to a lower intensity group. See statin intolerance pathway in Figure 1.

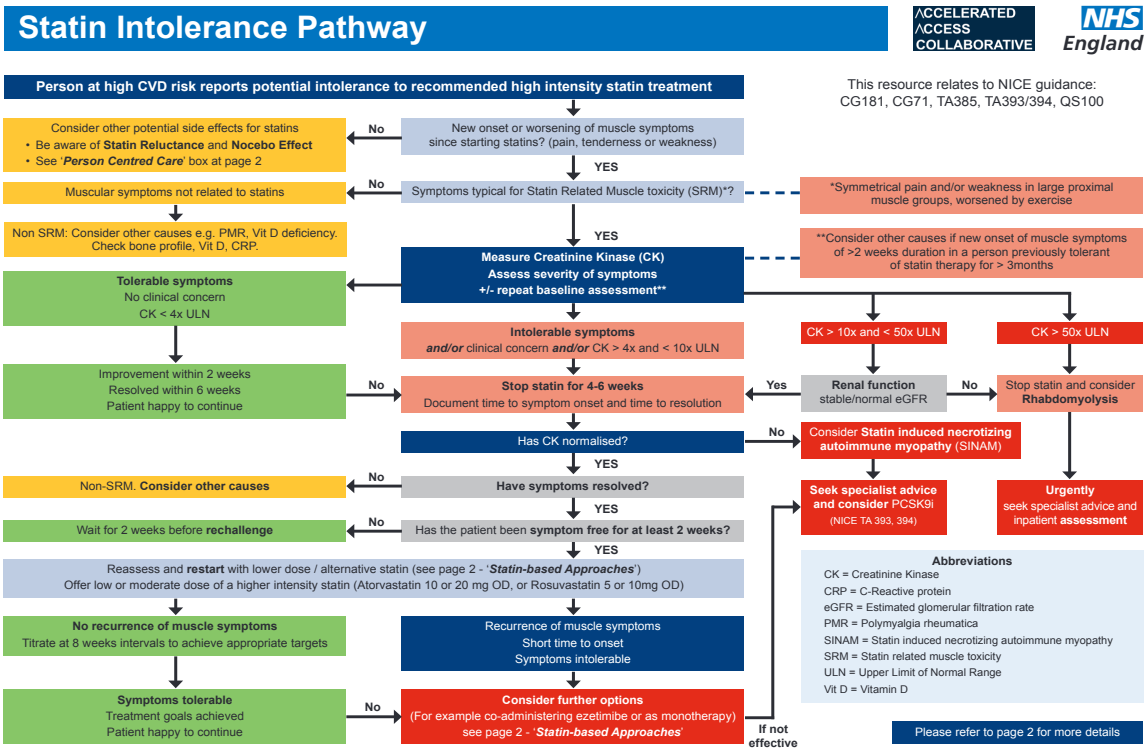


Figure 1: Statin intolerance pathway (NICE, 2014).

1.5 The Nocebo Effect

The placebo effect is a positive reaction to an inert substance or intervention. Up to 50% of the efficacy of a drug can be caused by a placebo effect (Weihrauch 2000). Conversely, the nocebo effect, is the negative equivalent of undesirable effects from placebos (Häuser et al. 2012). The nocebo refers to symptoms and/or physiological changes that follow the administration of an inert or active substance that the patient believes to be an active drug. 'Nocebo' is also commonly used to describe negative non-specific effects of active treatment in everyday use (Häuser et al. 2012) and is the definition that will be used in this thesis. The term nocebo differentiates the noxious or distressing effects of a placebo (Barsky et al. 2002). The effect size of placebo in controlled trials can be modest in meta-analysis but larger in studies of placebo analgesia, (Vase et al. 2002). In meta-analysis of nocebo magnitude a large effect size has also been shown (Petersen et al. 2014). There are fewer empirical studies investigating the nocebo effect compared to the placebo effect. The nocebo effect has been shown to manifest as a variety of symptoms such as pain, nausea, breathlessness, pruritus, depression (Wolters et al. 2019). A nocebo

effect with one treatment has been shown to transfer when starting a different treatment and so potentially could disrupt adherence to other therapies (Kessner et al. 2013). Understanding the nature of this phenomenon is important to understand its impact on everyday healthcare and to develop effective ways to manage and reduce it.

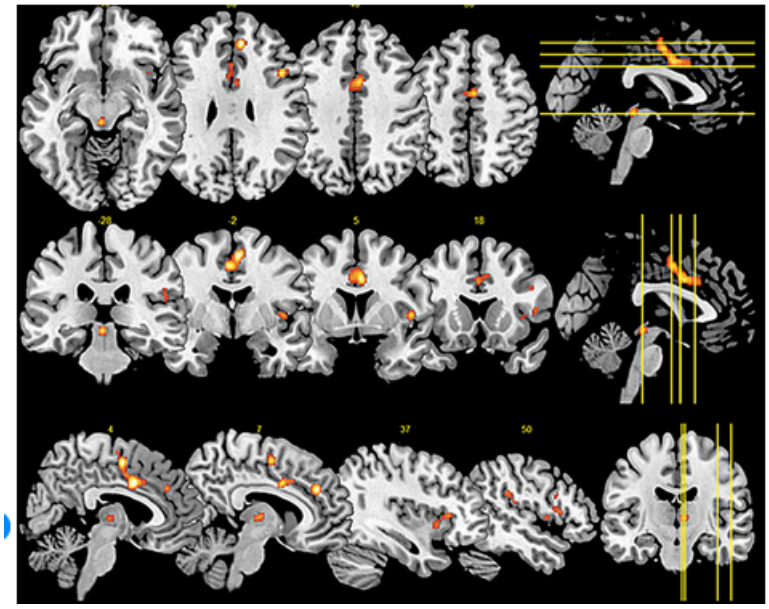


Figure 2: An example of a 'Meta-analysis of brain imaging data showing the regions activated (yellow/orange) and deactivated (green) during nocebo hyperalgesia. (Frisaldi, Shaibani & Benedetti, 2020) p. 7).

The neurobiological mechanism of a nocebo effect is also less well researched and less established than the placebo effect. Research has mainly focussed on pain rather than other types of nocebo symptoms (Mestre 2020). The nocebo effect can be verified objectively on imaging tests. Expectation and learning both have been shown to modulate pain pathways (Blasini et al. 2017). Nocebo effects are shown to trigger physiological changes in pain perception supporting the view the nocebo effect is not merely an exaggeration of existing symptoms. In placebo studies, naloxone blocks placebo analgesia responses and conversely in nocebo studies, cholecystokinin antagonists resulted in disease dependent reduction in hyperalgesia. Both hyperalgesia and the hypothalmic pituitary adrenal axis activity are blocked by anxiolytic drugs suggesting a role of anxiety in nocebo responses. There is altered brain imaging after administration of a nocebo, see Figure 2 (Kong et al. 2008) and pain related

activation in the spinal cord after negative verbal suggestion (Colloca and Grillon 2014).

Neuroimaging of the brain has demonstrated that expectation can activate brain structures for symptom perception prior to any stimuli, leading to sensitization to perceived discomfort (Schedlowski et al. 2015). Anticipation of pain has a protective function, to avoid harm through the initiation of adaptive behaviour to survive (Palermo et al. 2015). Nocebo effects elicit physiological responses and so are difficult for an individual patient or physician to distinguish from true pharmacological symptoms.

1.6 N-of-1 or single case randomised designs

N-of-1 trials are multiple crossover trials, normally randomised and blinded conducted with a single participant. It has been shown that the nocebo effect might be hard for patients to discriminate from true pharmacological side effects. Randomised controlled trials are the gold standard for assessing the efficacy of pharmaceutical drugs. But the question of how far clinical trial results can be generalised is complex because there are differences in disease, treatment uses, response and individuals who are more at risk of side effects. In terms of side effects, extrapolating results about safety from clinical trials to real life is likely to be prone to error (Shaffer et al. 2018) and little comfort to a patient experiencing side effects. Traditional trials estimate the average effect of an intervention. Whilst evidence based medicine can apply scientific evidence to everyday circumstances (Kravitz et al. 2004) an n-of-1 trial is one way to evaluate the optimal treatment for an individual person. N-of-1 trials can test a treatment against other comparators such as other medicines or placebo. N-of-1 trials have been used in epilepsy for participants with recurrent seizures, the trials demonstrated the intervention drug to reduce seizures over standard care for individual patients (Margolis and Giuliano 2019) and reflected situations where individualised trials were clinically useful.

The n-of-1 method is not suitable for all situations. Trials using outcomes that occur infrequently would not have sufficient power to detect changes. The n-of-1 method is also not suitable if a credible placebo cannot be made, and interventions must be reversible with little carryover or allowing suitable washout periods between interventions. It is not suitable for a rapidly

progressing disease condition. As with traditional controlled trials, assessors and participants, are ideally blinded and randomised. The ethics of any deception must be considered and risk or harm of discontinuing an active treatment must be assessed. In a review of n-of-1 trials conducted in 2011, 108 n-of-1 trials were identified and in 67 trials the 448 participants were given the treatment information after the intervention (Gabler et al. 2011). It was found 44% of the trials gave the results in a t-test format, 55% as a graphic representation and 43% as a pooled analysis. After the trials completion, 54% of participants changed treatment consistent with the trials results, 38% of participants' treatment decisions was ambiguous with what their actual trial results showed and only 8% was inconsistent with the trials results. In regards to statins, a previous n-of-1 proof-of concept trial has been completed and one other trial has been recently published (Joy et al. 2014, Tudor et al. 2020, Herrett et al. 2017). These trials showed n-of-1 trials are suitable for testing statins and showed for myalgia no significant difference in symptoms of myalgia with statins compared to placebo. At least one other n-of-1 trials for statins is currently in progress (Tudor et al. 2020).

1.7 Rationale for thesis

Statins are an effective therapy to prevent and manage cardiovascular disease, yet statin intolerance among users is prevalent and can lead to non-persistence with therapy. Evidence from pooling randomised clinical trials suggests that in blinded trials rates of adverse symptoms with statins are equivalent to the placebo arms. It is unclear if adverse symptoms are a result of underlying medical conditions or other drug exposure or if it is caused by nocebo response to therapy and if so this might offer a possible alternative explanation for why there are high rates of side effects when people take non-blinded statins. This thesis presents an innovative n-of-1 trial, to deliver personalised results to the individual patient about their proportion of their side effects that are truly statin related and importantly determines whether this personalised data can help people to safely restart a statin. Further to this, the pooled results will indicate whether statin side effects are likely to be pharmacological, psychological or background symptoms. To support this research and understand if it is generalisable several sub-studies are also presented as well as a review, which

formulates a theoretical model for how nocebo awareness might mediate the nocebo effect.

1.8 Key objectives and hypothesis of this thesis

1.8.1 Hypotheses of n-of-1 trial

Hypothesis 1: that >30% of participants enrolling for the trial will complete it.

Hypothesis 2: Overall >50% of symptom burden is nocebo rather than pharmacological

The Nocebo proportion of side effects is defined in:

$$Nocebo\ proportion = \frac{Nocebo\ component}{Total\ side\ effect(Pharmacological + Psychological}$$

Hypothesis 3: that the majority of participants, at 6 months after completion, will either be taking statins or have declined statins for reasons other than perceived side effects.

1.8.2 Objectives of n-of-1 trial

This thesis will:

1. Develop a method for determining within an individual participant to what extent experienced symptoms are associated with the statin or nocebo effect.
2. Evaluate in a cohort of participants who have stopped statins because of adverse symptoms, in what proportion of them, the symptoms are truly due to the statin.

1.9 Cross-disciplinary approach

Nursing research aims to translate research into practice to make healthcare safer and more effective (Curtis et al. 2017). The methodology applied in this thesis extends beyond this one discipline to also include medicine, psychology and clinical trial methodology. These four disciplines facilitate innovative methodology and explore the problems from several different perspectives. Working across disciplines is challenging; the outcome of interest to different professions is sometimes complementary and sometimes divergent. However, this thesis is an opportunity to explore how disciplines with different perspectives that are traditionally siloed and highly specialised can come together.

1.10 Discussion

CVD is a major cause of death worldwide. Reduction of LDL cholesterol is shown to reduce risk of CVD events. Yet adherence to statins which are a treatment to reduce serum LDL cholesterol is poor. Non-adherence to statins leads to increased mortality and costs to healthcare systems. Interventions in healthcare to improve the utility of medical therapy are important as they have the potential to save lives. Statins are a safe medical therapy that is proven effective in the prevention and management of cardiovascular disease and relatively inexpensive. Yet, it appears the psychology of the patients who take medicines interferes with their persistence with them and this leads to preventable morbidity, mortality and extra health care costs. This thesis uses methodologies from medicine, nursing and psychology and a combination of qualitative and quantitative methods to explore this current problem. This thesis identifies possible solutions including an n-of-1 trial to examine for the individual participant the proportion of side effects with statins that are pharmacological, psychological or simply background symptoms, in order to understand the extent to which statins are the cause of side effects for the individual participant and to see if in the cases where statins are not the cause whether their result assists patients restarting a statin.

The nocebo effect is a less well-studied phenomenon than the placebo effect. One of the primary outcomes of the trial is to provide results to the patient about the proportion of their symptoms that are truly statin related to see if the results can influence individuals enough to restart a statin. Therefore, it is important to understand whether being made aware of the nocebo effect mediates the level of nocebo response. In chapter two of this thesis, in light of scarce literature on this phenomenon, a novel methodology is used to collate the literature on nocebo awareness in order to theorise whether being made aware of the nocebo effect is of benefit and leads to persistence with therapy. The review will qualitatively synthesise medical, nursing and psychological literature to develop a theoretical model of how a person's awareness of the nocebo effect may affect their nocebo response.

Chapter three highlights the trials methodology, chapter four presents the phone application used in the trial and provides evidence of its testing and preliminary validation, chapter five presents the trial data and chapter six

presents a qualitative study about patient experience of statins as well as public patient involvement (PPI) feedback. In conclusion, chapter seven is a discussion of the results.

2 Thematic synthesis: A proposed theoretical model to predict knowledge and awareness of the nocebo effect on the magnitude of the nocebo effect.

2.0 Chapter overview

Chapter one introduced the concept of the nocebo effect and provided empirical evidence from the literature about the phenomenon. The nocebo effect is a possible explanation for adverse symptoms experienced with certain medical therapies, which are misattributed as pharmacological rather than psychological consequences of taking tablets. These side effects, if caused by a nocebo effect but wrongly attributed to the pharmacology of the drug might lead to people stopping effective therapies unnecessarily. This makes it of clinical importance and leads to the question: if people are made aware of the nocebo effect how does this influence their response to medical therapy? Does it have any influence and if so, does it attenuate or exacerbate side effects? Counter-intuitively, studies show that even if a person is aware they are taking a placebo it does not always stop them experiencing a placebo effect (Schafer et al. 2015, Colloca and Howick 2018) and so in terms of the nocebo effect, it may also not be clear-cut what effect awareness of the nocebo effect has on the nocebo effect itself. It is an important question because if, for example, awareness of the nocebo effect attenuated its effect, this would be a potentially cost-effective strategy to promote persistence with medication through communication of the risk of the nocebo effect to '*at-risk'* patients.

The topic of this review has reaching consequences, an initial scoping of the literature showed existing research had not directly explored the impact of awareness of the nocebo effect on how it mediates response to medical therapy. Therefore, in this chapter, a systematic search of the literature was undertaken; relevant and 'high-quality' studies on this topic were selected and synthesised using a Thematic Synthesis (Thomas and Harden 2008) to abstract generic themes which were used to generate a theoretical model of how knowledge of the nocebo effect might be predicted to mediate it. Thematic synthesis can generate theories leading to hypotheses to test through future experimentation. This type of review method is used to generate a theoretically testable model to explain, predict and understand more about the nocebo effect, which is an under researched phenomenon.

This chapter begins by explaining why a qualitative review is the most appropriate approach to explore this topic. There is a range of established qualitative review methodologies and in this chapter, they are briefly discussed and the reasons why, of them all, Thematic Synthesis was chosen for this review. The details of the methodology for the review are outlined and for transparency examples of the stages of the review process are presented. The results and a theoretical model derived from the literature are presented and components of the model are described. In summary, it is theorised what effect nocebo awareness has on the nocebo effect and how communication about the nocebo effect could be optimised. The review then discusses the findings in light of the existing literature and gives limitations of the method and future recommendations.

Review question: Does awareness of 'Nocebo' phenomena mediate response to medical therapy?

2.1 Qualitative synthesis

Qualitative synthesis or qualitative systematic review aggregate or summarise data on a topic and used adapted qualitative analysis methods to interpret it. Traditional systematic reviews bring together primary research studies to quantitatively answer specific questions. Qualitative synthesis relates to methods for reviewing and combining the findings of qualitative literature. This type of approach of synthesising qualitative studies has been used in health care particularly for investigations relevant to patients' perception of their care. Qualitative literature is traditionally thought of as literature that explores points of view or experiences. The main criticism of methods attempting to synthesise primary qualitative research is the studies are context dependent and not generalisable.

'To summarise qualitative findings is to destroy the integrity of the individual projects on which such summaries are based, to thin out the desired thickness of particulars (…) and ultimately to lose the vitality, viscerality and vicarism [sic] of the human experiences represented in the original studies.' (Page 366) (Sandelowski et al. 1997)

Yet, collectively exploring studies and considering different contexts allows researchers to understand why people do not always act in the same way and

compels a level abstraction to human experience to build theory and could provide new insights into areas of clinical practice that are at an impasse.

2.2 Methods of qualitative synthesis

There are multiple existing methods for undertaking qualitative synthesis:

- Grounded formal theory has been adapted for use in synthesis and involves simultaneous phases of data collection and analysis which is an inductive approach allowing theory to emerge from the data (Eaves 2001).
- Meta-ethnography (Noblit and Hare 1988) which translates themes or concepts between qualitative studies to develop overarching concepts and explore contradictions between studies, to create a grounded theory or line or argument whilst exploring diverse methodological approaches rather than 'like' with 'like' as with grounded formal theory.
- Textual narrative synthesis provides a description of the current 'state of knowledge'. It synthesises studies of different types, provides descriptions and compares differences between studies. But this method is less effective at highlighting similarities between studies (Lucas et al. 2007).
- Meta-study is an exhaustive analysis of theory, method and findings to examine differences across the literature of a substantive area. (Sandelowski, Margarete and Barroso 2003)
- Meta-narrative is a method to summarise research findings by synthesising studies with many different theories to make sense of large data sets (Greenhalgh et al. 2005).
- Critical interpretative synthesis is an adaptation of grounded theory and meta-ethnography which allows integration of qualitative and quantitative data through an interpretative process, ecological triangulation and framework synthesis (Dixon-Woods et al. 2006).
- A thematic synthesis uses abstract constructs and generates hypotheses that can then be tested through quantitative approaches (Thomas and Harden 2008).

2.2.0 Thematic Synthesis

Often the above methods overlap with some using different terminology for an equivalent approach. This current review followed a thematic synthesis approach for the following reasons:

- The method is practical and unlike some of the other more labour-intensive methodologies it is achievable within the resources available.
- Thematic synthesis employs a formalised process for identifying and developing themes. It is used widely across qualitative analysis of varying epistemological approaches to qualitative analysis.
- Initially descriptive themes generated through the analysis of primary studies closely represent those primary studies providing transparency of method. Then with the development of analytical themes, which go beyond the primary focus, specific questions can be answered, and new hypotheses generated. This method is reproducible, and the validity of the results can be assessed.

2.2.1 Quantitative studies within a thematic synthesis

Traditionally, quantitative studies such as clinical trials are excluded from thematic synthesis and considered separately. However, without including the quantitative studies that shape the direction of qualitative exploration, there are hidden theoretical 'black holes' in any interpretation. Therefore, quantitative studies were also included and synthesised qualitatively, using line-by-line coding of the results sections. Including these studies in the interpretation is more labour intensive than analysing just the qualitative studies but allows the full diversity of the topic to be captured (Noyes et al. 2019).

For this review, because there are known biases to quantitative studies, clinical trials and cohort studies were rated based on a Critical Appraisals Skills Programme (CASP) checklist (Critical Appraisal Skills Programme 2019). Poor quality clinical trials and cohort studies were excluded to limit bias. Qualitative studies were also rated and described using the qualitative CASP checklist, but they were not excluded if they scored poorly because specific details provided in a qualitative study publication vary according to the publishing journal and its criteria. Authors of qualitative studies who publish in medical journal may have a more restricted word count or be limited in terms of the amount of data and description they can provide. Therefore, details critical for the appraisal of the

paper may not be reported (Soilemezi and Linceviciute 2018). Qualitative papers that were identified by CASP or the reviewers deemed as being of a particularly poor standard were assessed using a sensitivity analysis that looked at the contribution of the paper to the review (Carroll and Booth 2015) and excluded it if judged not to contribute sufficiently to the analysis.

2.3 Thematic Saturation

Thematic saturation is reached when further analysis of further research papers reveals no new themes or interpretation. In this case, analysis of further papers reveals no new themes about how awareness of the nocebo effect is associated with the nocebo effect. Unlike a meta-analysis, where to avoid bias, searches of the literature should be exhaustive, for thematic synthesis the analysis is not predictive, it provides an interpretative explanation (Thomas and Harden 2008). Therefore, it is not technically necessary to find all studies but rather to find different and diverse studies, to ensure conceptual saturation is achieved. Seeking contradictory findings among studies that give maximum variation is more important than finding multiple studies with similar findings. However, extensive searches were undertaken to achieve maximal diversity of the literature to assist in achieving greater levels of abstraction and increased confidence that thematic or conceptual saturation had been reached.

2.4 Method

2.4.0 Scoping

Initial searches determined that no relevant systematic reviews of qualitative studies had previously been conducted. Initial searches determined the amount, variety and quality of qualitative and quantitative research undertaken on the awareness of the nocebo effect and adapted methods to ensure the review was feasible.

2.4.1 Objectives

- To explore how the nocebo awareness mediates the nocebo response.
- To examine the possibility of deriving a higher order of analysis from the existing literature.
- If awareness of the nocebo effect attenuates its effect, to theorise about the optimal ways in which to provide this information to participants.

2.4.2 Inclusion Criteria

Study:

1) Qualitative or questionnaire-based/survey studies (including interviews or focus groups, expert recommendations or a qualitative study reported as part of a quantitative study) or 'high-quality' quantitative studies including randomised controlled trials and cohort studies (which scored above 2 on the first two questions of the CASP)

2) Primary research data only

3) Literature in last 7 years (2013-2020)

4) Studies involving humans.

5) Studies published in English language or published with English translation.

6) Studies looking at mediators of the nocebo effect

7) Quantitative studies, if published in journals with impact factor ≥4.5 (this adaption was made to make the review feasible within the resources available).

Study participants:

8) Adults - 18 years or older.

2.4.3 Exclusion Criteria

1) Non-qualitative and non-survey study designs and 'poorer-quality' quantitative studies

2) 'Experimental psychology' investigating the structure or function of the nervous system and brain through techniques such as electrophysiology.

3) Reviews, editorials, letters, case studies, design/methodology and baseline only research papers

4) Studies including only children or adolescents

5) Studies including vulnerable populations (prisoners, mentally incapacitated, drug addicts etc.)

6) Studies looking at the placebo effect only

7) Quantitative studies published in journals with impact factor < 4.5 (to be initially excluded but abstracts will be read and any that cover topics not already covered in the review may be included)

2.4.4 Literature Search

Research databases were searched using specific and inclusive search terms.

Search terms: Nocebo OR ‘Negative Placebo’ (exact phrase)

2.4.5 Search strategy

- Using thesaurus terms – e.g., MeSH etc.
- Free-text terms – e.g., Nocebo or Negative placebo

2.4.6 Search sources

The following databases and resources were searched:

- CINAHL
- Embase
- PubMed
- Psycinfo
- Web of Science
- JSTOR
- Project MUSE

2.4.7 Data Collection & Analysis

1. One researcher (FW) carried out all the database searches.
2. One researcher (FW) then undertook title and abstract scanning to gather all relevant studies that met the eligibility criteria.
3. In response to scoping, to make the number of studies more manageable, the review excluded quantitative studies in journals where the impact factor was < 4.5, as it was considered likely that higher impact publications were of better quality.
4. Quality of each included study was assessed using the appropriate CASP tool for the study design. The second coder (MF) assessed quantitative papers; minor discrepancies in ratings were discussed and adjusted. If agreement could not be reached a third coder resolved the conflict (MSS). Quantitative studies were excluded if the scores on the first two CASP questions were ≤ 2. The initial searches (July 2018) were updated to include 2018 - 2020 and 6 additional studies were identified. These were not second coded as it was considered that reasons for earlier discrepancies between coder had been identified and sufficient consensus reached that meant going forward coders would be likely to score consistently.

5. FW reviewed full text of the studies considered to be relevant. Full text PDFs of relevant studies were imported to Nvivo 12.0 qualitative software (QSR International Pty Ltd 2018). FW undertook line-by-line coding of textual findings from the results section of the abstract main paper, using Nvivo software to organise the coding. Due to the amount of coding, FW organised line-by-line codes in terms of 'domain summaries' to identify themes between different studies that appeared linked to create 'descriptive themes' (examples of stages of analysis are included in the results section).
6. FW then created 'analytical' higher order themes through abstracting the descriptive themes from their context.

2.4.8 Quality of literature

Each primary research study was assessed for quality using the relevant Critical Appraisal Skill Programme (CASP) checklist (Critical Appraisal Skills Programme 2019). All studies were assessed using CASP and RCTs were second coded (except for the papers identified during the updated search) and discrepancies in scoring were discussed and resolved.

2.5 Results

2.5.0 Included studies

Figure 3 is a CONSORT diagram of the search results. Of the 26 identified publications, 2 RCTs and 1 cohort study were excluded because of scoring less than 4 on the first two questions of the CASP scale, leaving 23 studies in the review. See raters discrepancy of CASP assessment in Appendix 1. One further qualitative paper was excluded following sensitivity analysis because it was deemed not to contribute to the overall analysis. See Table 2, for characteristics of the 22 included studies.

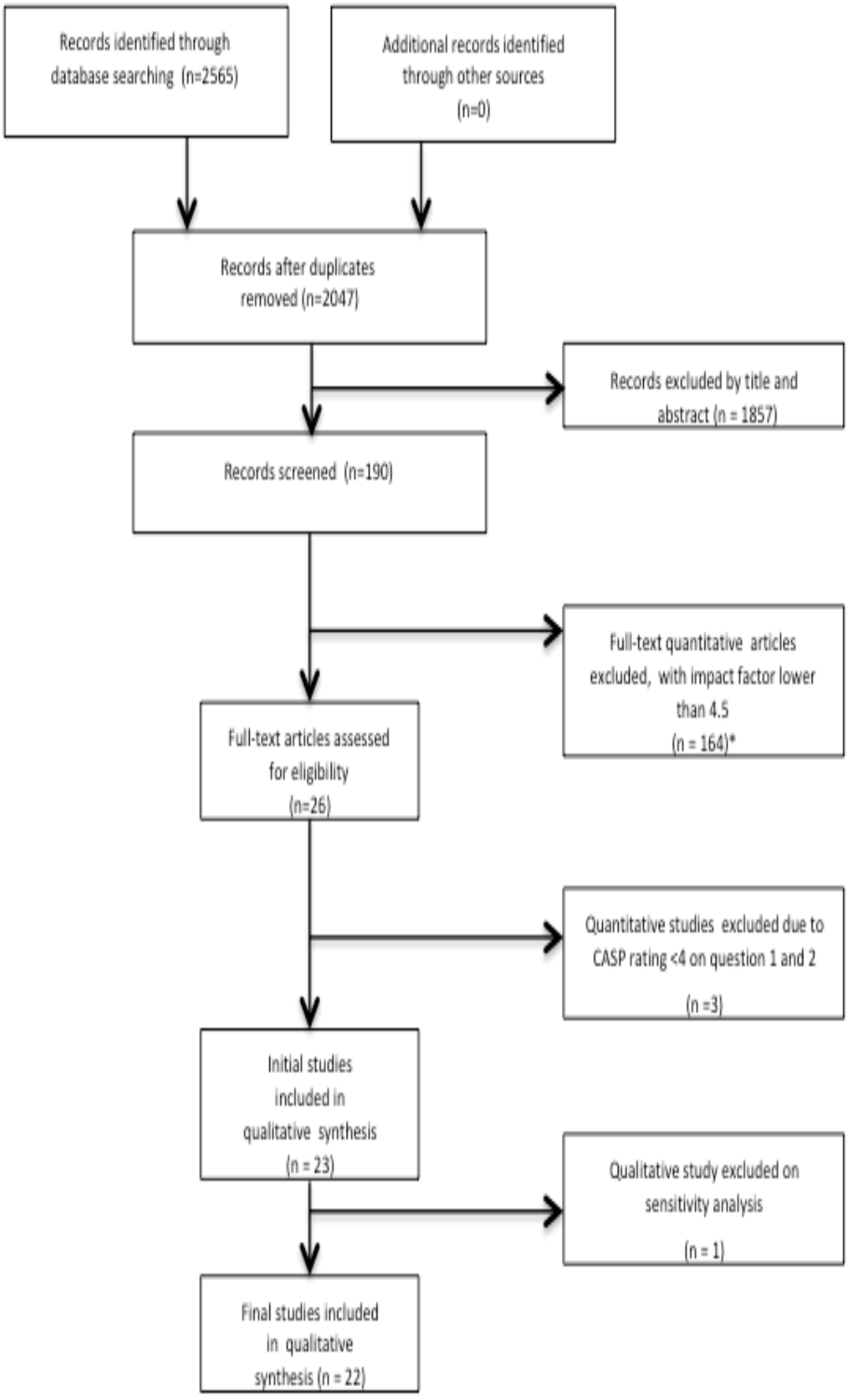


Figure 3: CONSORT diagram of the literature review searches and screening of papers for suitability for inclusion

Table 2: Characteristics of included studies

Author Year Country	**Type of Nocebo Investigation**	**Participant type Participants Number Mean age**	**Impact factor CASP score**	**Study type/Study design**	**Summary of results (relevant to nocebo awareness)**
(Aslaksen et al. 2015) Norway	Heat pain stimulation with medication (analgesia, placebo, nocebo, none) and information about effect of medication (analgesia, hyperalgesia, medical cream, none)	Healthy volunteers 142 23 years old	6.0 18	RCT/Multi-factor between subject design	Interaction trial by group was significant (F [10, 260]=15.19, P<0.01). No significant group differences in pre-test (all P>0.75). Pain highest post-test 2, in hyperalgesia suggestion groups compared to the analgesia suggestion group regardless of whether the hyperalgesia group received the analgesic cream or the inert cream (both P<0.01).
(Bräscher et al. 2017, Colagiuri and Quinn 2018)	Report (TV report on adverse health effects of electromagnetic field (EMF) or neutral report) Followed by ratings in tactile stimuli with sham Wi-Fi in 50% of trial.	Healthy volunteers 65 25 years old	5.026 18	RCT/ Between subject design	EMF film group rated film as being more personally relevant (U=314.0, p=0.012; r=.32) and worrisome (U=314.0, p=0.012; r=.28) compared to the control film. In EMF group sham Wi-Fi led to higher ratings of tactile stimuli F(1,61)=4.8, p=0.032) especially in participants with higher levels of somatosensory amplification compared to the control group (β=-1.157,p=0.003).
Colagiuri and Quinn 2018 Australia	Pain conditioning (Placebo, nocebo, none) paired with sham TENS treatment during training. In test phase, pain assessed with and without treatment at equal pain stimulation.	Healthy volunteers 65 20 years old	5.424 17	RCT/Mixed model Between and within	Nocebo hyperalgesia extinguished significantly less than the placebo analgesia (n_p^2 =.106, $F_{1, 37}$=4.39, P=0.043). Nocebo treatment group compared to controls had heightened treatment-evoked anticipatory anxiety (n_p^2 =0.77, $F_{1,56}$=4.65, P=0.035) and skin conductance rating (autonomic arousal) (n_p^2 =0.77, $F_{1, 54}$=4.51, P=.038). Negative correlation between anticipatory anxiety and extinction (indicating higher anticipatory anxiety

Author Year Country	Type of Nocebo Investigation	Participant type Participants Number Mean age	Impact factor CASP score	Study type/Study design	Summary of results (relevant to nocebo awareness)
					associated with less extinction) r=-0.372, 95% CI=-.589 to-.140, P<0.05. Neither expectancy ratings nor anticipatory anxiety ratings significantly correlated with extinction ratio.
(Colagiuri et al. 2015) Australia	Pain conditioning (Complete reinforcement, partial reinforcement, none). In training phase, pain stimulation was surreptitiously increased on nocebo trials in 62.5% in partial reinforcements group. In test phase pain stimuli equivalent across groups.	Healthy Volunteers 135 20 years old	5.424 17	RCT /Between subject design	Nocebo hyperalgesic effect induced in both partial reinforcement group relative to controls ($F_{1,114}$=4.26, P=.04, η^2_p =.04) and in complete reinforcement groups relative to controls ($F_{1,114}$=20.2, P=.001, η^2_p=.15) and failed to extinguish. Strength of nocebo hyperalgesia significantly greater in complete reinforcement group compared to partial reinforcement group (Mean difference=4.76, $F_{1, 114}$=5.57, P=.02, η^2_p =.05). No main effect of trial no significant group by trial interaction ($F_{10,4,1710}$=1.41, P=.13, η^2_p =.01 and $F_{20,9,1710}$=.93, P=.55, η^2_p=0.2 respectively) indicating once established hyperalgesic effects did not extinguish. Strong concordance with expectancy and nocebo hyperalgesia in both complete reinforcement (b=.350, $t_{1,33}$=3.94, P<.001, unique R^2=.307) partial reinforcement (b=0.474, $t_{1,36}$=6.77, unique R^2=.547) and the control group (b=.517, $t_{1,38}$=4.84, P<.001, Unique R^2=.370).
(Crichton and Petrie 2015)	Explanation of symptoms (Nocebo explanation, biological explanation). Both groups exposed to two sessions of	Healthy volunteers 66 28 years old	5.026 16	RCT / Between subject design	Significant group by time interaction in relation to symptoms F(2, 126)=15.56, p<0.001, η_p^2=.20, and to symptom intensity F(2, 126)=9.51, p<0.001, η_p^2=0.13. The biological explanation group had significant increase from

Author Year Country	Type of Nocebo Investigation	Participant type Participants Number Mean age	Impact factor CASP score	Study type/Study design	Summary of results (relevant to nocebo awareness)
New Zealand	infrasound and audible wind farm sound. Preceding first exposure both groups watched a video purporting health risk posed by wind farms. Then in pre-session 2 nocebo vs. biological explanation given.				baseline to session 1 in both number of symptoms experienced (p=0.0002) and reported symptom intensity (p=0.046) and that increase from baseline was sustained during session 2 (ps<0.001). In contrast, the nocebo explanation group reported an increase from baseline to session one in symptoms and symptom intensity (Ps+0.008) but a decrease in symptomatic experiences from session one to session two with symptoms and symptoms intensity returning to baseline levels during session two (Ps<0.001). During session one, participants in both groups reported deterioration in mood from baseline. Mood deterioration and increase in symptoms maintained in biological explanation group while in nocebo group they returned to baseline. In relation to mood, significant group by time interaction in terms of negative mood (F(2,126)=9.74, P<0.001, η_p^2=0.13 and positive mood F(2,126)=13.13, p<0.001, η_p^2=0.17. Post hoc analysis showed in biological explanation group there was a significant increase from baseline in negative mood during session one (p=0.002) and session two (P<0.001) and also significant decrease from baseline in positive mood during both session (ps<0.001). In terms of the nocebo explanation group there was a significant increase in negative mood

Author Year Country	Type of Nocebo Investigation	Participant type Participants Number Mean age	Impact factor CASP score	Study type/Study design	Summary of results (relevant to nocebo awareness)
					(p=0.026) and a significant decrease in positive mood (p<0.001) from baseline to session one with mood returning to baseline levels during session two. The biological explanation group had significantly greater negative mood and lower positive mood than nocebo explanation participants during session two (p<0.001).
(Dunne et al. 2014) Ireland	Perceptions of generic medicines	GPs and pharmacists 78 Mean age not specified	2.075 15	Semi- structured interviews	Participants (health professionals) believed most adverse symptoms with generics was nocebo rather than actual
(Evers et al. 2018) The Netherlands	Expert recommendations	'Internationally recognised placebo researchers' 29 Age not reported	13.744 13	Survey	Experts believed in the importance of informing patients about the nocebo effect
(Geers et al. 2019) United States	Affect induction (positive vs. neutral) Verbal suggestion (no suggestion vs. suggestion of pain increase). Positive or neutral affect induced by watching video clips. Inert	Healthy Volunteers 147 20 years old	6.029 17	RCT/Multi factor between subject design	Main effect of pain rating, $F(6, 858)=255.79$, $P<0.001$, $\eta_p^2=0.64$, pain rating increase as contact with pain stimulus progressed. Pain rating x affect induction interaction $F(6, 858)=2.50$, $P<0.05$, $\eta_p^2=0.02$ and a pain rating x verbal suggestion interaction $F(6, 858)=3.03$, $P<0.05$, $\eta_p^2=0.02$. Verbal suggestion and affect induction influenced pain

Author Year Country	Type of Nocebo Investigation	Participant type Participants Number Mean age	Impact factor CASP score	Study type/Study design	Summary of results (relevant to nocebo awareness)
	cream with or without verbal suggestion that it could increase pain during cold pressor test.				ratings. Participants in the neutral-affect condition who received pain increase suggestion reported greater pain on each of the 5 pain ratings compared with participants who received no suggestion (P's <0.05, Cohen's d's=.38,.43,.42,.37 and .36 respectively). In the positive-affect conditions with pain suggestion, the pain ratings of the positive-affect participants demonstrated no evidence of nocebo hyperalgesia across the 7 pain ratings (P's>0.7, Cohen's d;s=0.01. 0.05, 0.01, 0.04, 0.01, 0.04, 0.02 respectively). Although hyperalgesic effect after the neutral-affect induction, there was no evidence for nocebo hyperalgesia after the positive-affect induction.
(Harvie et al. 2015) Australia	Pain free range of motion in neck using virtual reality (VR) headsets (20%<actual rotation, equal to actual physical rotation, 20%>than actual rotation	Volunteers with neck pain 24 45 years old	4.902 20	RCT/within-subject repeated measures design	Large overall effect of visual-proprioceptive feedback (condition) on pain-free range of motion $F(2,94)=18.9$, $p<0.01$, $\eta_p^2=0.29$). All pairwise comparisons were significant (ps<0.01). When vision understated true rotation, pain-free range of motion was increased and this was a medium-sized effect p=0.006, d=0.67. When vision overstated neck rotation pain free range of motion decreased and this was a large effect, p=.001, d=0.80. Specifically, during visual feedback that understated true rotation, pain-free range of motion was increased by 6% (95% confidence interval or CI= [2%,11%]) during visual feedback that overstated true rotation, pain-free range of motion decreased by 7% (955 CI=[3%,11%]).

Author Year Country	Type of Nocebo Investigation	Participant type Participants Number Mean age	Impact factor CASP score	Study type/Study design	Summary of results (relevant to nocebo awareness)
(Kampermann et al. 2017) Germany	Physicians' beliefs about antidepressants effectiveness	Physicians 87 45.8 years old	2.776 18	Survey	For occurrence of side effects majority of physicians attributed substantial role to patient expectation and experiences.
(Krüger et al. 2018) Germany	GP experience of statin therapy	General practitioners 16 Age not reported	4.434 13	Interviews	GPs regarded negative media coverage and nocebo effect as having a significant impact on statin therapy.
(Mills et al. 2019) Australia	Caffeine withdrawals symptoms in moderate to heavy coffee drinkers in open, blinded and deceptive reduction groups.	Healthy volunteers 48 20.8 years	4.738 18	RCT/Between subject design	The open reduction group reported more pronounced caffeine withdrawal symptoms than the deception group on the days with greatest discrepancy between actual and informed caffeine dose. The rate of increase in caffeine symptom withdrawal questionnaire scores in the open reduction group was 6.95 points per day ($t(126)=5.04$: $p<0.001$; 95% CI=4.22-9.68). The rate of increase in the deceptive reduction group was 2.12 points per day, an estimated rate of increase that was significantly lower than the open reduction group (estimate difference=-4.83; $t(126)=-2.48$;$p=.03$; 95% CI=-9.46-0.98). Also, the estimated rate in blind reduction group was 2.73 points per day, a rate of increase that was significantly lower than open reduction group (estimated difference =-4.12; $t(126)=-2.11$; $p=.038$; 95% CI=-7.98—0.25). The

Author Year Country	Type of Nocebo Investigation	Participant type Participants Number Mean age	Impact factor CASP score	Study type/Study design	Summary of results (relevant to nocebo awareness)
					difference in rate of increase between the blind reduction and deceptive reduction was not significant (estimated difference=0.71; t(126)-0.37; p=0.715; 95% CI=3.91-5.34).
(Nestoriuc et al. 2016) Germany	Post-operative breast cancer patients with hormone receptor positive breast cancer due to start adjuvant hormone therapy. Structured assessment of side effects, side effect expectations, quality of life and adherence. Measured 1-week post operatively, 3-months and 24-months.	Oestrogen hormone receptor positive breast cancer patients 111 56 years old	13.926 18	2-year prospective clinical cohort study	Pre-treatment expectations significantly predicted long-term side effects with adjuvant hormone therapy and quality of life. Relative risk of side-effects after 2 years of therapy was higher in patients with high negative expectations at baseline than those with low negative expectations at baseline (RR=1.833, CI 95%, 1.032-3.256).
(Niederstrasser et al. 2015) Canada	Delayed onset muscle soreness (DOMS) protocol on targeted arm then next day rated pain in targeted and non-targeted arm during lifting task. Using DOMS protocol pain is not expected in non-targeted arm.	Healthy volunteers 82 23 years old	5.424 21	Cohort	Catastrophising and fear of pain prospectively predicted pain experience in non-targeted arm. The estimated coefficient for the covariate indicated participant who experienced higher levels of pain on the targeted arm also reported more intense pain on the nontargeted arm both in session 1 ($\beta_A^{(1)}$=.79, p<.001) and in session 2 ($\beta_A^{(2)}$=.99, P<.001). Main effect of catastrophizing, higher levels of pain catastrophizing predicted greater levels of pain on first lift at session 1 ($\beta_{PCS}^{(1)}$=.46, p<.01) when lifting task was not expected to be painful. Pain ratings at session 2 increased significantly for individuals with high levels of

Author Year Country	Type of Nocebo Investigation	Participant type Participants Number Mean age	Impact factor CASP score	Study type/Study design	Summary of results (relevant to nocebo awareness)
					pain rating for the non-targeted arm at session 2. Follow-up analyses revealed that there were no differences between high and low catastrophizers (i.e., 2 SD above average versus 2 SD below average) on the first (mean = .31, SD = .61, t(322) = .51, P = .61) and second (mean = 1.00, SD = .59, t(322) = 1.7, P = .09) lifts at session 2, whereas high catastrophizers reported significantly greater pain during lift 3 at session 2 (mean = 1.7, SD = .61, t(322) = 2.78, P < .01). High catastrophizers' pain increased over repeated lifts. Pain-related fear predicted greater levels of pain on the first lift at session 1 (β_{FOP}[1]=.74, P<.0001). A change of 1 SD in pain-related fear score was associated with an increase of .34 SD in reported pain on the first lift at session 1). Follow-up analyses revealed that individuals with high pain-related fear (i.e., 2 SD above average) reported greater pain on the first lift (mean = 2.96, SD = .69, t(306) = 4.3, P < .0001), second lift (mean = 2.82, SD = .68, t(306) = 4.17, P < .0001), and third lift (mean = 2.68, SD = .7, t(306) = 3.81, P < .0005) than individuals with low pain-related fear (i.e., 2 SD below average).
(Petersen et al. 2014) Denmark	Open-hidden capsaicin (Hyperalgesia) Open-hidden lidocaine and no treatment.	Patients with post-thoracotomy	6.029 20	RCT/Within subject repeated measures with qualitative	No significant difference in ongoing or evoked pain between the open capsaicin group, hidden capsaicin group and control group. Similar level of positive and negative emotion in open capsaicin group. No significant difference

Author Year Country	Type of Nocebo Investigation	Participant type Participants Number Mean age	Impact factor CASP score	Study type/Study design	Summary of results (relevant to nocebo awareness)
		neuropathic pain 18 57 years old		experiential method.	in expected pain levels across the 3 groups. The intensity of the negative emotional feelings reported in the open administration of capsaicin was on average 3.3 (1.7) on the M-VAS compared with 3.2 (2.5) for the intensity of positive emotional feelings. Hence, the patients reported a similar intensity of positive and negative emotional feelings after the open capsaicin administration.
(Pouillon et al. 2019) Europe	Clinical recommendations for prevention and management of nocebo effect in biosimilar treated Inflammatory Bowel Disease patients	Healthcare professionals Not reported Age not reported.	7.731 15	Clinical recommendations	Recommended education about biosimilars that should be tailored to the individual patient and positive framing information to reduce the nocebo effect.
(Roderigo et al. 2017) Germany	Treatment Suggestion (Analgesia, neutral, Hyperalgesia) and Stress protocol (Stress induced or neutral). Saline treatment administered and perceived urge to defecate and pain in response to rectal distension assessed.	Healthy volunteers 120 26 years old	6.029 20	RCT/Multifactor between subject design	Negative information increased urgency to defecate in stressed group only. Stress by itself had no significant independent effect on distension-induced urgency (ANCOVA main effect of stress: $F = 2.12$, $P = 0.15$). Treatment information, on the other hand, emerged as a significant factor (main effect of information: $F = 9.06$, $P < 0.001$) but was significantly modulated by psychological stress (interaction stress x information: $F = 3.38$, $P < 0.05$). Post hoc testing revealed that only in the stressed group, positive information significantly reduced urgency when compared to neutral information ($P = 0.025$). Negative information, on the other

Author Year Country	Type of Nocebo Investigation	Participant type Participants Number Mean age	Impact factor CASP score	Study type/Study design	Summary of results (relevant to nocebo awareness)
					hand, significantly increased urgency in the stressed group when compared to neutral information in the stressed group (P= 0.026)
(Shin et al. 2015) South Korea	Attitudes towards communication of side-effects	Oncology patients, caregivers and oncologists 725 Patient – caregiver dyads) 134 oncologists Patient: 60.2 years old	3.430 15	Survey	Patients and caregivers thought they should be informed about all drug side effects regardless of risk.
(Skvortsova et al. 2019) The Netherlands	Oxytocin nasal spray vs. placebo group All groups received verbal suggestion that TENS device would regulate pain (heat pain); when a green stimuli the TENS would decrease pain, with a yellow stimuli TENS would be inactive and with a red stimuli TENS would increase pain. Sham	Healthy male volunteers 80 23 years old	5.424 20	RCT/Between subject design	Main effect of the cue colour on the pain ratings ($F(1.41, 104.61) = 61.71$, $P < .001$, $\eta p2 = .46$), while the main effect of the group ($F(1, 74) = 2.31$, $P= .13$, $\eta p2 = .01$) and the group x cue colour interaction ($F(1.41, 104.61) = .63$, $P= .48$, $\eta p2 = .01$) were nonsignificant. Nocebo hyperalgesia elicited, extinction over test phase but did not return to baseline levels. Oxytocin did not influence nocebo hyperalgesia or extinction.

Author Year Country	Type of Nocebo Investigation	Participant type Participants Number Mean age	Impact factor CASP score	Study type/Study design	Summary of results (relevant to nocebo awareness)
	TENS device. Conditioning training phase: the stimuli coupled with pain levels congruent to the verbal suggestion. In test phase pain stimuli always medium.				
(Thomaidou et al. 2020) The Netherlands	In induction phase, sham TENS machine paired with higher pain stimuli (7/10) in continuous conditioning group, 70% in partial conditioning and 50% in sham conditioning. All were at lower pain stimuli (5/10) and paired on evocation. During the attenuation phase, pain stimulation decreased in nocebo trials for counterconditioning group (2/10) while pain remained equivalent on all trials for extinction group.	Healthy volunteers 122 Range 18-35 years	6.029 19	RCT/Multi factor Between subject design	Both complete and partial reinforcement induced nocebo hyperalgesia. But complete reinforcement was more potent. Counterconditioning was more effective than extinction in attenuating nocebo hyperalgesia but neither complete nor partial reinforcement resulted in resistance to extinction. Conditioning with partial reinforcement resulted in more resistance to counterconditioning. Significant interaction between the partial reinforcement and sham group and the magnitude of nocebo responses (F(1,72) 5 20.58, P,0.001, η^2 =50.22), between the CRF and sham group and the magnitude of nocebo responses (F(1,71) 5 45.22, P, 0.001, η^2 =0.39), and between the PRF and CRF groups and the magnitude of nocebo responses (F(1,95) 5 7.28, P 5 0.008, η^2 =0.07). These results indicated that conditioning with PRF and with CRF were both effective in inducing significant nocebo responses, with CRF producing a significantly larger nocebo response as compared to PRF.

Author Year Country	Type of Nocebo Investigation	Participant type Participants Number Mean age	Impact factor CASP score	Study type/Study design	Summary of results (relevant to nocebo awareness)
					The analysis revealed a significant interaction between the counterconditioning and extinction groups and the reduction of nocebo responses ($F(1,95) = 6.51$, $P = 0.012$, $\eta^2 = .06$ indicating higher efficacy of counterconditioning compared with extinction. A nonsignificant interaction effect showed no significant difference in resistance to extinction between conditioning with PRF and CRF ($F(1,46) = 0.63$, $P=0.43$, $\eta^2=.01$). Significant difference in the resistance to counterconditioning between conditioning with PRF vs CRF ($F(1,47)$ 5 4.99, $P = 0.03$, $\eta^2 = .09$), PRF leads to more resistance to counterconditioning than CRF.
(Verrender et al. 2018) Australia	Video (alarmist video about electromagnetic field exposure vs. control video). Each participant had repeated measures of open label and double blinded radio frequency ON and OFF provocation trials	Healthy volunteers 44 22 years old	5.026 15	RCT/Within and between subject design	Symptoms increased in open label radio frequency ON compared to OFF. Overall, participants had significantly higher increases in symptom scores in the RF-ON condition (Median = 17.00) compared to the RF-OFF condition (Median = − 0.50), T=77.00, z=−4.476 (corrected for ties), N - ties =40, p< .001, ES =0.71. The symptom scores in the RF-OFF condition were equal between the alarmist (Mean = 11.59 Median =− 3) and control (Mean = 11.45 Median = 0) video groups, validating the comparison of symptom difference scores between the two groups.

Author Year Country	Type of Nocebo Investigation	Participant type Participants Number Mean age	Impact factor CASP score	Study type/Study design	Summary of results (relevant to nocebo awareness)
					No difference in double-blind trials of radio frequency ON or OFF. Participants in alarmist video group had increased symptoms and state anxiety and risk perception compared to controls. The symptom difference score was higher in the alarmist (Median = 25.50) compared to the control (Median = 5.00) video group, and the interaction between symptom difference score and video group was significant, U =159.50, z=− 1.738, p=.041 (one-tailed), ES =0.26
(Webster et al. 2018) United Kingdom	Side effect risk influences expectations	Healthy volunteers 1003 Median 41.0 years old	2.847 18	Survey	Higher expectations of side effects for 'very common' and 'common' side effects, expectations fell sharply for 'rare' and 'uncommon' side effects. Higher expectations associated with women, ethnic minorities, 'household illness; less educated, high perceived sensitivity to medicine and negative beliefs about medicines.

The key stages of the Thematic Synthesis are shown in Figures 4-8. The initial stage of the analysis involved the coder immersing themselves in the research paper, and coding every line of text for all meaning, one sentence could be coded into multiple descriptive themes (Figure 4-5). The next stage involved refining themes by looking for similarities of codes between papers and in different research papers and creating new codes to capture the meaning of grouped codes (Figure 6-7). Figure 8 is included for illustrative purposes of the interconnection between themes. Lastly, themes are abstracted from the context to develop a theoretical line of argument about the research question based on what the pattern of themes identified.

Figure 4: Inductive themes from line-by-line coding – (within the Nvivo software all generated themes have a 'data trail' and clicking on a theme or code will show quotation from the source research article the paper was originally coded from).

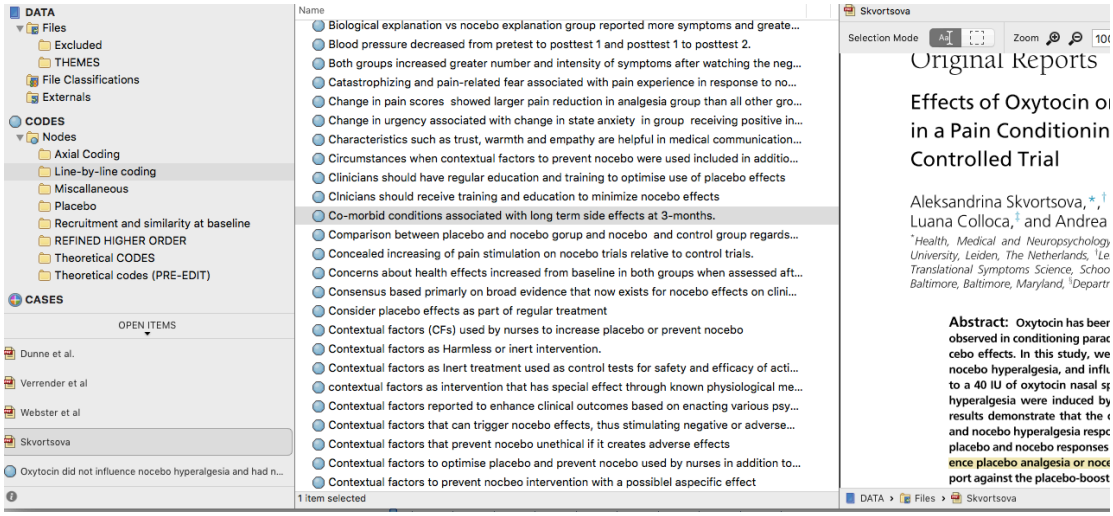


Figure 5: Illustrates example of line-by-line coding of an extract of published paper in Nvivo

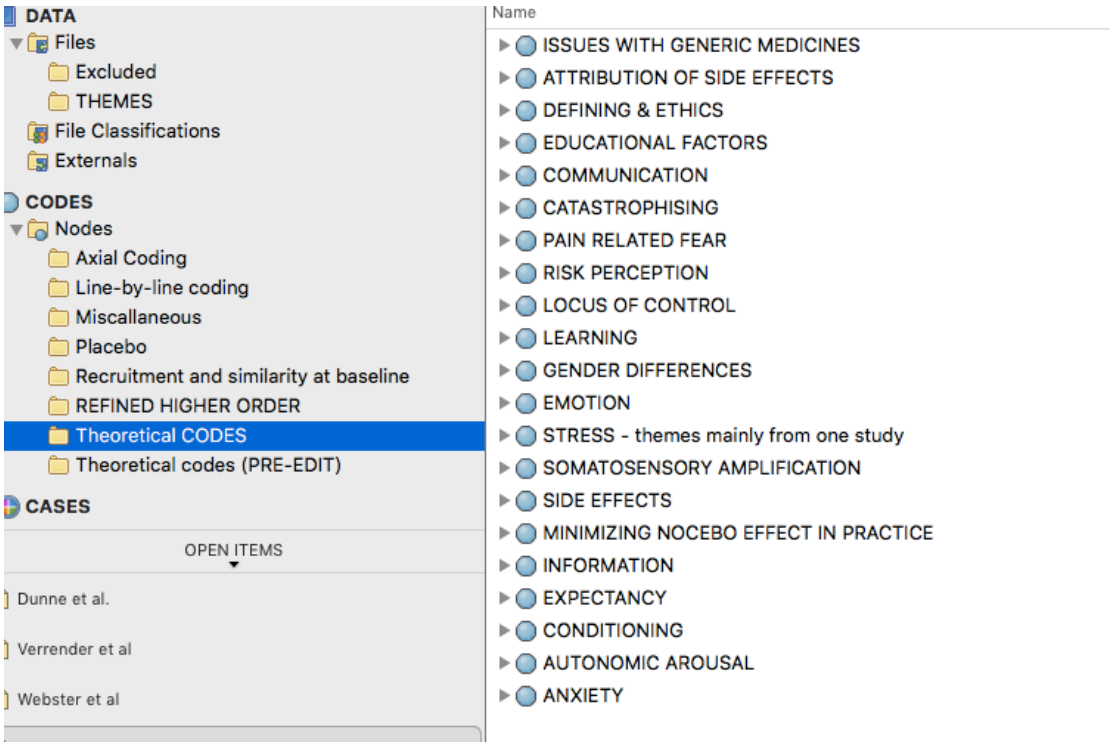


Figure 6: Overarching domain summaries or containers for line-by-line coding.

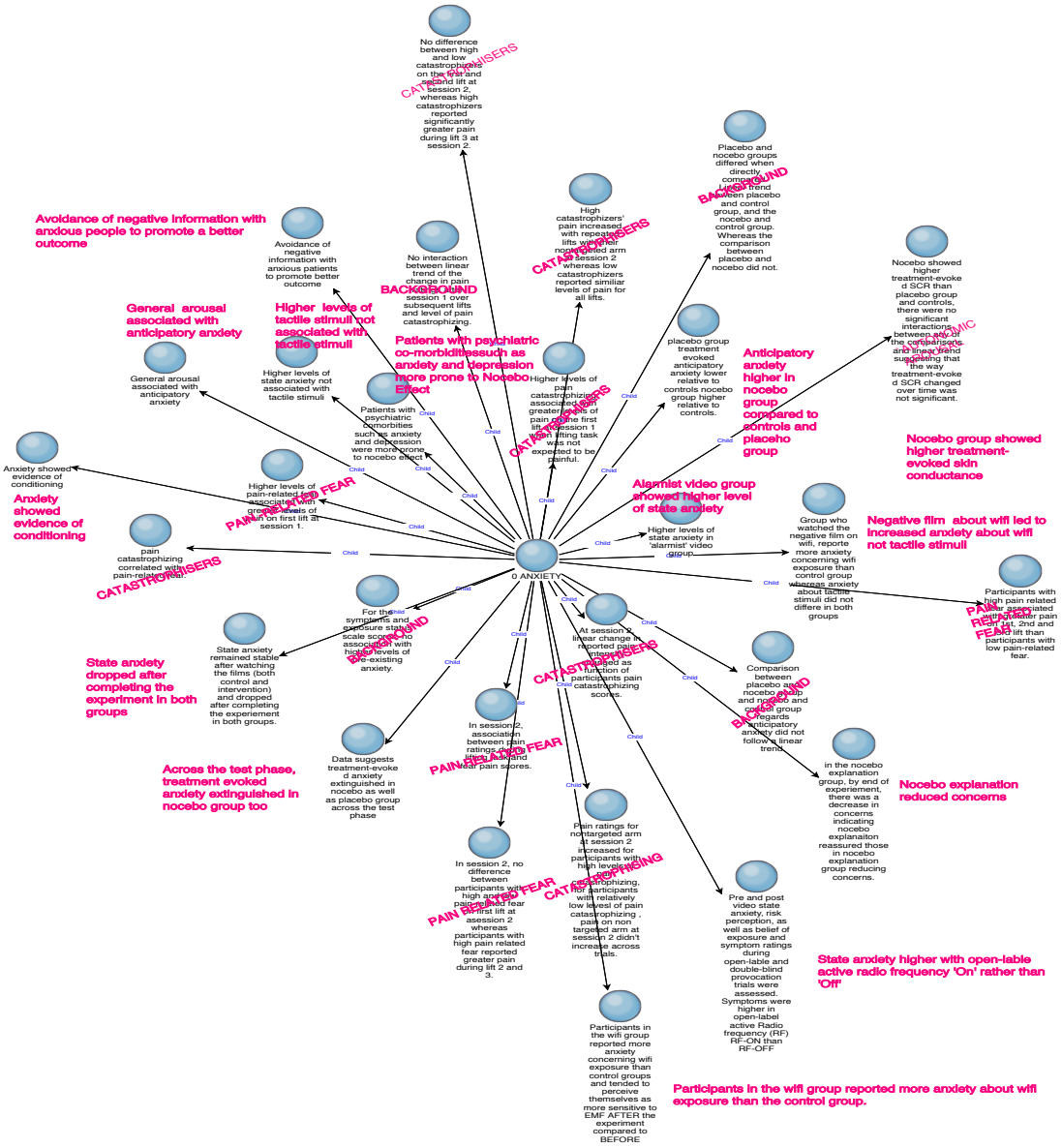


Figure 7: Axial codes inductively generated from line-by-line coding (Coder reviews coded texts for a code/theme. Relevant sub-themes are reworded to better capture the meaning, codes more relevant to other areas are flagged for recoding e.g. in 'pain-related fear' and 'background' information that is descriptive but adds no value to the analysis is flagged for removal).

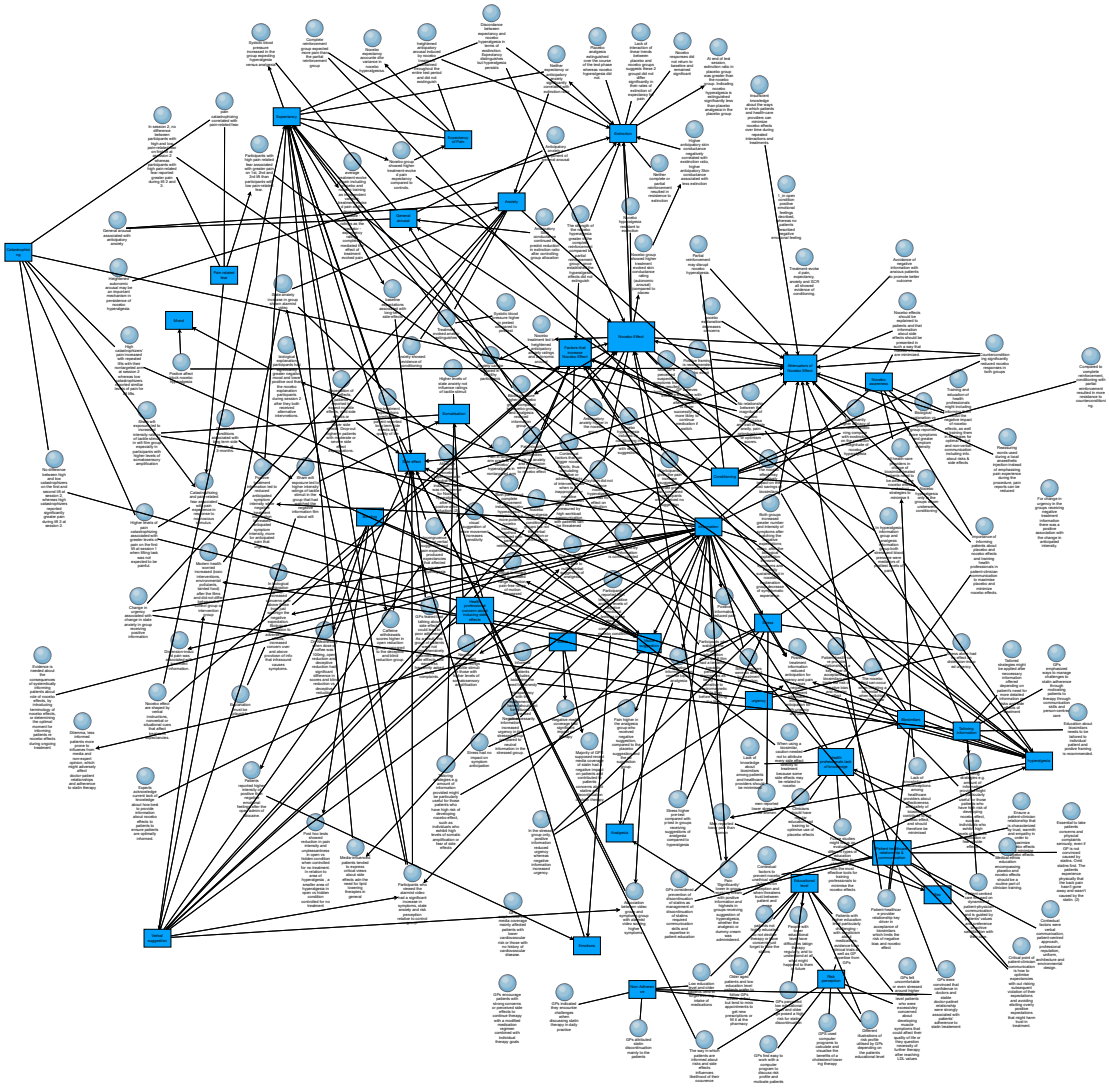


Figure 8: Map of overall themes of the review

In the forthcoming section, please refer to Table 2 for the details of the studies relevant to each commentary.

2.5.1 'Any person' is susceptible to a nocebo effect

The nocebo effect can be induced in healthy volunteers (Asklaksen et al, Bräscher et al, Colagiuri & Quinn, Crichton & Petrie, Geers et al, Mills et al, Roderigo et al, Skvosova et al, Thomaidou et al, Verrender et al). This review identified studies where a variety of nocebo effects were induced, using information, conditioning or a combination of techniques to induce nocebo symptoms including pain (Asklaksen et al, Colagiuri & Quinn, Crichton & Petrie, Geers et al and Skvosova et), tactile stimuli (Bräscher et al), caffeine withdrawal, a well-proven pharmacological withdrawal syndrome (Mills et al)

and urgency to defecate (Roderigo et al). In one study, comparing open vs. blinded treatment, open treatment exacerbated adverse symptom reporting compared to blinded trials (Verrender et al.).

2.5.2 Expectancy of side effects predicts actual side effects

Following a delayed onset muscle soreness protocol, pain from lifting in the targeted arm predicted pain from lifting in the participants' non-targeted arm, on a task not expected to cause pain in the non-targeted arm (Niederstrasser et al. 2015). In post-operative breast cancer patients who were starting adjuvant hormone therapy pre-treatment expectations predicted long-term side effects (Nestoriuc et al. 2016). In a pain conditioning RCT, nocebo expectancy accounted for variance in nocebo hyperalgesia (Colagiuri et al b).

2.5.3 Negative suggestion of side effects predicts side effects

In a heat pain stimulation RCT, pain was lower in the group receiving cream with positive information and higher in the group receiving a suggestion of hyperalgesia even when the cream administered was itself an analgesic (Aslaksen et al). In contrast, positive framing of information was shown to reduce pain in a rectal distension RCT (Roderigo et al. 2017). Experts recommend positive framing of information to reduce the nocebo effect when swapping patients to biosimilars (Pouillon et al. 2019).

2.5.4 Suggestion of risk increases belief in perceived risk

Positive treatment information led to reduced anticipated symptom intensity (Roderigo et al. 2017). Whilst participants who viewed an alarmist video about electromagnetic fields had a significant increase in symptoms, state anxiety and risk perception compared to the control video group (Verrender et al). In participants with chronic neck pain who had their neck rotation surreptitiously manipulated through the use of virtual reality headsets, those who were led to believe neck rotation to be greater, had increased sensitivity to movement (Harvie et al, 2015). Participants who watched negative information about Wi-Fi had a tendency towards perceiving themselves as being more sensitive to electromagnetic fields than before watching the film (Brascher et al).

2.5.5 High level of arousal is associated with nocebo effect

In participants who watched an alarmist video about electromagnetic field exposure versus a control video, there was an increase in state anxiety as well as symptoms (Verrender et al). In a heat stimulation RCT, where groups were given different information about their medication, blood pressure increased in the group expecting the hyperalgesia compared to those expecting analgesia (Aslaksen et al). Blood pressure and stress mediated levels of pain after (Aslaksen et al). In an RCT, conditioning with pain stimulation and sham treatment, higher anticipatory skin conductance rating was associated with less extinction of the nocebo effect (Colagiuri and Quinn). In a RCT of rectal distension, for the stress-induced group only, negative information increased urgency to defecate (Roderigo et al). Furthermore, general practitioners in Germany considered those with pre-existing anxiety conditions may be more pre-disposed to the nocebo effect (Kruger et al).

2.5.6 Negative mood is associated with the nocebo effect

In an RCT, inducing positive affect in participants prevented nocebo hyperalgesia symptoms compared to the control group (Geers et al). Conversely, in an RCT, where participants were given a biological explanation of adverse symptoms rather than a nocebo explanation as the cause; the biological explanation group had more negative mood and lower positive mood (Crichton and Petrie 2015). In an experiment that failed to induce the nocebo effect, level of negative emotional feelings was at an equivalent level to the positive emotional feelings (Petersen et al) but not greater unlike in studies where the nocebo effect was induced.

2.5.7 Negative suggestion is associated with somatisation

After watching negative information about electromagnetic fields, participants were led to believe an electromagnetic Wi-Fi field was set up in the room they were in, it was in fact sham Wi-Fi but led to higher intensity of ratings of tactile stimuli in those who had watched the negative information versus the control video and also increased the ratings of tactile stimuli in those with higher levels of somatosensory amplification (Brascher et al).

2.5.8 Nocebo effect is resistant to extinction

A conditioned nocebo effect is resistant to extinction (Colagiuri and Quinn, Colagiuri et al, b.); when the stimuli are no longer paired with the pain participants continue to associate pain with the stimuli. What is more, in an RCT using counterconditioning with positive stimuli to attempt to extinguish the nocebo effect, the learnt association between pain and the stimuli was stronger if induced through partial rather than complete reinforcement.

2.5.9 Awareness of the nocebo effect

In an RCT, participants watched a video about the health risk of wind farm infrasound (low frequency noise) and then listened to these sounds (Crichton and Petrie). Compared to baseline, adverse symptoms and negative mood increased after exposure to the sounds. One group were then provided with a nocebo explanation of their symptoms whilst the other group were given a 'plausible' biological explanation. In the group given the nocebo explanation it led to both adverse symptoms and negative mood decreasing and returning to baseline levels, compared to the biological explanation group. Experts on the nocebo effect have recommended making patients aware of the nocebo effect and training health professionals to communicate about the nocebo effect to patients (Ever et al).

2.5.10 The derived theoretical model

The theoretical model developed during this review was initially grounded in the literature but then the final model was abstracted, as displayed in Figure 9. It is proposed that any person can be prone to the nocebo effect. Multiple studies in the review successfully induced a nocebo effect in healthy volunteers. It is proposed people might perceive themselves as more at risk from a therapy if a person has a high expectancy of developing harm such as side effects from a particular therapy or if an individual is exposed to information about the risk of harm from the therapy. It is proposed that having a higher perceived risk of harm from a therapy increases negative mood, increases levels of autonomic arousal and somatisation and these are all associated with a nocebo effect. Once a nocebo effect is learnt it is hard to extinguish particularly if the learning schedule is partial rather than complete. Therefore, it is proposed that a person may not get adverse symptoms every time with a therapy, but partial reinforcement may make the nocebo effect harder to extinguish. It is proposed

that awareness of the nocebo effect reduces perception of risk by offering an alternative explanation for why symptoms might have occurred, and so negative mood, somatisation and autonomic arousal reduce. However, this model theorises that if a nocebo effect is already established or 'learnt' it may be hard to disrupt. Therefore, it is predicted that the best time to inform a patient about the risk of a nocebo effect is before or during the initiation of therapy.

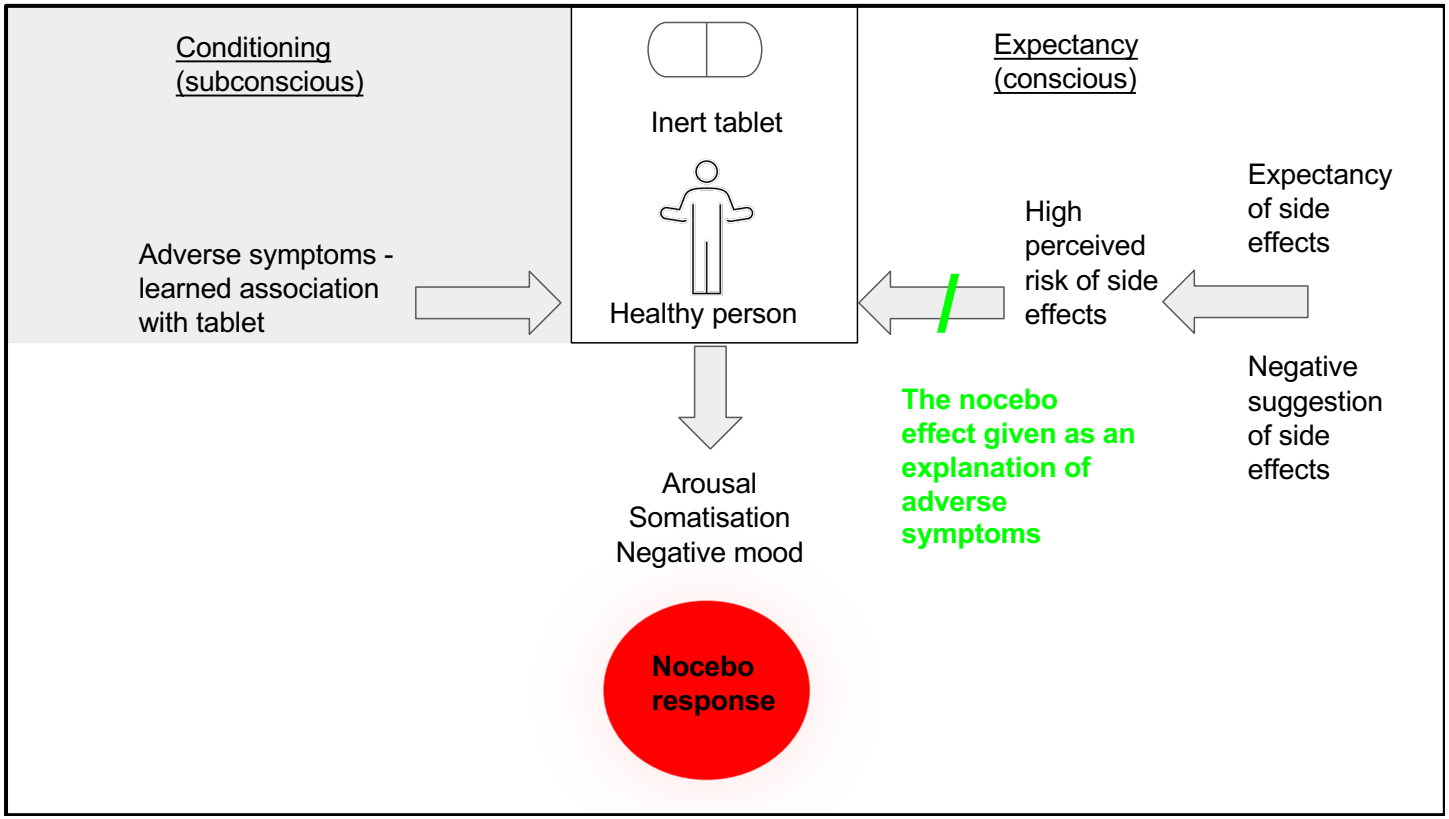


Figure 9: Theoretical model of how nocebo awareness could attenuate the nocebo effect

**In Figure 9 'Inert tablet' refers to an inert drug or an active drug where response is not to the drugs pharmacological properties*

2.6 Summary of chapter

This review explored the factors associated with the nocebo effect and how nocebo awareness influences response to the nocebo effect. It derived a higher order of analysis from the existing literature about how awareness of the nocebo effect mediates response to the nocebo effect. A theoretical model was developed which predicts that nocebo awareness attenuates the nocebo effect. This review also theorised the optimal circumstances to inform a patient about the nocebo effect. This model proposes that the optimal timing for communicating the risk of a nocebo effect is before therapy is initiated and if a nocebo effect is already established it may be harder to extinguish, so prevention may be important.

This review found that the information participants receive influences their expectations about treatment, emotional response, level of anxiety and also their experience of treatment whether the treatment was a nocebo or even active analgesia. Even with active analgesia negative suggestion can reverse the analgesic effect. Health care professionals' communication and the patients' awareness of the nocebo effect were proposed as important possible avenues for future research into ways to reduce nocebo effect as well as positive framing and reducing negative information about medicines. Negative information was shown to increase somatisation particularly in those prone to somatosensory amplification. Importantly, the environmental conditions for the nocebo effect might be more probable in a clinical context, where less support is available (increasing anxiety levels) and treatment is unblinded, than in research studies. In addition, the findings of this review that partial reinforcement leads to a harder to extinguish and more robust nocebo effect raises concerns for clinical practice. If adverse symptoms occasionally occur at the same time as a person is taking a therapy, it might actually be unintentionally leading to a harder to extinguish learnt association between the therapy and the adverse symptom compared to if a participant got an adverse symptoms every time they took the therapy.

3 Methods and recruitment for the SAMSON trial

3.0 Chapter Overview

There is a high discontinuation rate among patients who take statins because of suspected side effects. The literature review proposed that awareness of the nocebo effect might assist patients with attenuating its effect. The Self-Assessment Method for Statin side-effects Or Nocebo (SAMSON) trial was designed to help patients determine the aetiology of symptoms previously ascribed to statins and determine if their side effects are truly drug-related or not. This chapter details the methodology for the SAMSON trial. Other trial of this kind for statins include a proof of concept trial (Joy et al. 2014) which did not include a no-tablet arm and so was unable to measure background symptoms by comparing 'on tablets' vs. 'nothing'. Furthermore, treatment periods were just 3 weeks and inclusion criteria defined symptom onset within 3 weeks - possibly an insufficient interval for side effects to emerge. Joy's trial also only assessed myalgia. In addition, the recently published StatinWise trial (Herrett et al. 2021) again did not include a no tablet arm and also only looked at myalgia. This chapter also describes the setting, participants eligibility and the assessments for the SAMSON trial. The study protocol, data processing and analysis plan are described. Ethical considerations are reviewed, and the recruitment process is outlined. The SAMSON trial has a unique trial design that no other n-of-1 trial of statins has used before. I discuss my intellectual involvement in the development of the protocol design and analysis.

3.1 Research Design

This trial is an n-of-1, randomised placebo double-blind cross over trial, which includes randomised unblinded no treatment periods.

3.2 Rationale for the research design

Despite there being clear evidence of the benefits of statins, many patients experience side effects when taking them. Some people's side effects may not be pharmacologically related because adverse symptoms occur equally with blinded placebo as with blinded statins. Perceived side effects could be a result of an aversion to the statin or background symptoms. Therefore, blinded periods of statin and placebo as well as unblinded no treatment periods allow

participants to determine for themselves whether side effects are background symptoms that occur even when not taking anything and also to discriminate whether or not symptoms are statin related by having blinded periods of statin and placebo.

3.3 Qualitative Study

See chapter 6 for a description of the qualitative study methodology. Patients who were not eligible or not interested to take part in the main trial, were invited to participant in interviews about their experience of statins and side effects to understand popular experience of statins.

3.4 Setting and Participants

See study protocol in Appendix 2. See Figure 10 for the trial's eligibility criteria.

Figure 10: SAMSON trial eligibility criteria

Inclusion criteria for SAMSON trial: • Aged 18 years or older • Previously taken one or more statins • Withdrawn from statins because of perceived side effects • Developed side effects within 2 weeks of initiation • Clinical indication for statins for primary or secondary prevention of CVD or dyslipidaemia
Exclusion criteria for the SAMSON trial: • History of any condition that causes chronic pain • History of severe mental illness • Currently taking fibrates • History of statin intolerance with creatine kinase elevation greater than 5 times the upper limit of normal • History of statin intolerance with anaphylaxis • History of statin intolerance with myalgia and rise in serum creatine kinase • History of statin intolerance with rhabdomyolysis • History of statin intolerance with liver function abnormalities, defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times the ULN • Currently taking anti-retrovirals with known interaction to statins • Currently taking any drug with known interaction to statins

- Pregnant or breast feeding
- Side effects taking longer than 2 weeks to present
- In clinical judgement of study doctor, participant should not be enrolled

3.5 Assessments

All participants installed the SAMSON application on a mobile phone, personal computer or tablet device.

Starting from Month 0 (Baseline) until Month 12 three questionnaires were completed on a monthly basis (see in Appendix 13-15):

- the EQ-5D-3L (Devlin and Brooks 2017) an established health related quality of life questionnaire with normative data;
- the Treatment Satisfaction Questionnaire for Medication (TSQM) version 1.4 (Atkinson et al. 2004). a validated side effects questionnaire
- the 'confounding life events questionnaire' designed by the study team to capture confounding factors that might affect quality of life and well-being. The study team developed it based on key areas known to effect well-being. It was not validated but was created to determine if adverse symptoms were confounded by particular positive or negative life events.

The study team initially planned to use the complete TSQM 1.4 questionnaire but feedback from the cognitive interviews (see Chapter four) and from trial participants indicated that 3 of the 4 domains were not suitable in terms of statins or were non-sensical in the context of a blinded trial. Permission was granted by the license holders to use just the relevant side effect domain on the scale. A file note was recorded for audit purposes. All questionnaires used in the trial were explored in cognitive interviews. See Chapter Four for the development of the app and its validation.

3.6 Data Capture

Data capture and randomisation were performed using InForm. InForm Integrated Trial Management is a web-based data entry system. It is widely used across the pharmaceutical industry for this purpose. The study team, overseen by the Imperial Clinical Trials Unit, developed the specifications for the system which were built and supported by the information and

communications technologies team at Imperial College London. These systems were then formally checked using test scripts and passed all tests, prior to going live. During the trial the InForm system was updated from version 4.6 to 6.0. Using InForm creates an audit trail essential for monitoring purposes. All data was inputted to InForm by the research nurse except phone scores which were input by the patient and upload to the InForm database by the InForm team.

3.7 Procedure

3.7.0 Recruitment

Participants were either invited by their health care professional or self-referred. All participants initially spoke to the same research nurse, myself, who pre-screened them for eligibility. Those who were eligible and wished to take part in the trial were sent information sheets (see Appendix 3 for information and consent forms for the trial) and given at least 24-hours to consider participation before they were booked to attend a screening appointment.

3.7.1 Scheduling first visit

Participants who decided to participate were sent a letter and a map confirming their appointment. They were reminded by telephone the day before their appointment. All face-to-face visits were conducted in the Peart-Rose Research Unit at Hammersmith Hospital, London.

3.7.2 Source data

When booking the screening appointment written consent was sought to request source data from the participant's GP about their medical history (see letter and source data request form in Appendix 4).

3.7.3 Informed Consent

When participants arrived at the Peart-Rose Research Unit, they were greeted by the research nurse, myself. I confirmed their identity, recorded contact details including their next of kin and established their allergy status. I went through the trial information sheet, confirming they had read and understood it. I answered any questions. The study doctor came in and also went through the

information with them and answered any questions. The study doctor took written informed consent. The original signed consent form was filed in the site file and copies were filed in the research notes and the clinical notes. A copy was given to the participant.

3.7.4 Screening Visit

After written informed consent was received, I completed the case report form (CRF) with the participant using the source data provided by the GP (see CRF template in Appendix 5). Height, weight and blood pressure were measured and an optional blood sample for cholesterol profile was offered if the participant had not had a recent test (within the last 6-months) at their GPs. After completion the study doctor reviewed the CRF, and determined whether:

- The participant met the eligibility criteria.
- It was safe for the participant to restart a statin.
- The participants symptoms were assessable.
- The participant was on any medications that could interact with a statin.

The study doctor confirmed in writing that they were happy for a participant to be randomised. In the event they were not happy for a patient to take part, the doctor explained sensitively the reason to the participant and documented this on InForm. A letter was sent to the participants GP describing the visit and the outcome (randomisation or screen failure).

3.7.5 Randomisation

I undertook randomisation using the InForm system. 60 randomisation codes were generated by an independent Imperial Clinical Trials Unit statistician prior to the start of the trial and uploaded to InForm. I entered the participant's details and date of consent. The next randomisation code was selected automatically by InForm. Confirmation of randomisation and trial identification number were generated by InForm and signed by the study doctor.

3.7.6 App installation

Following randomisation, the app was installed on the participant's smartphone. Training was given on its use and a test score was sent by the participant to

check he/she was able to use it correctly and to confirm the server was receiving scores from their electronic account.

3.7.7 Safety Reporting

Every participant was given an identification (ID) card that listed their details and the contact details for the trial team. Participants were advised to keep the card on their person and the nurse confirmed during the monthly call that the participant still carried their card and also reminded them that the research team's telephone number was on the ID card. Participants were encouraged to inform the study team about any symptoms they deemed related to the trial and the study nurse monitored daily phone scores and contacted participants if scores were 'high' (indicating adverse symptoms) or if there were no scores returned for several days. During monthly telephone contacts, participants were asked about adverse events (AEs) and changes to their medication regime. All AEs were reported on InForm including those deemed unrelated to the trial. All AEs were coded using the latest version of the Medicines Dictionary for Regulatory Activities to standardise medical terminology for reporting. AEs classed as serious were reported to the Sponsor within 24-hours and in the event any SAEs had been classed as Suspected Unexpected Serious Adverse Reaction (SUSARs) these would have also been reported to the UK regulatory authority (MHRA) within 7-days. Expectedness of events was determined using the reference safety information from the Summary of Product Characteristics (SmPC) for the Ranbaxy Atorvastatin 20mg.

3.7.8 Dispensing Investigational Medicinal Product (IMP)

The Guys and St Thomas' Production pharmacy repackaged Atorvastatin 20mg film coated Ranbaxy tablets and for the trial (see Figure 11 showing a photograph of the Atorvastatin 20mg OD and matched placebo tablets and Figure 12 shows examples of the actual containers for medications used during the trial).

Figure 11: Examples of samples of spare non-blinded Atorvastatin 20mg OD tablets alongside the matched placebo (containers in the picture were not the labelled containers of medicines used in the trial).

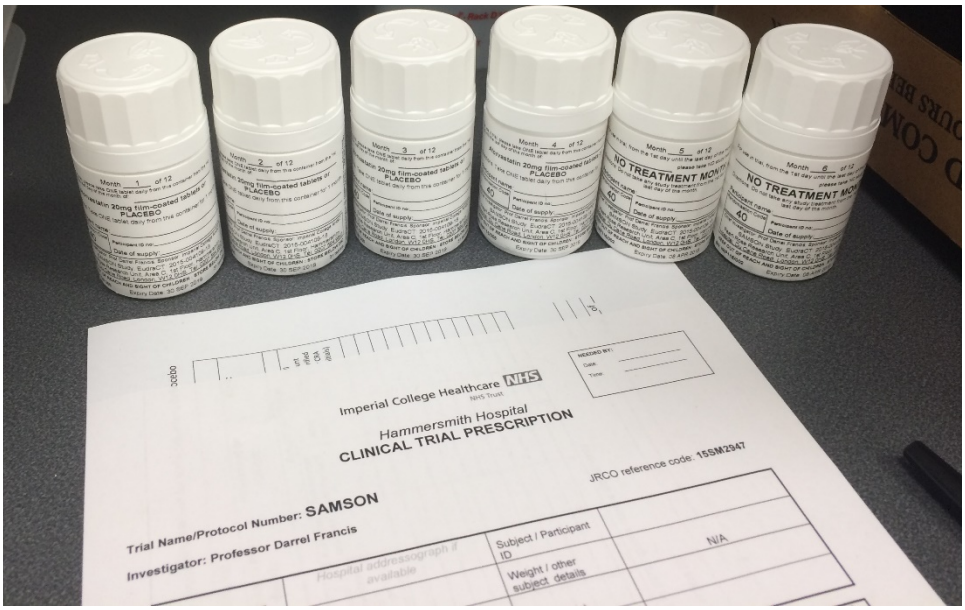


Figure 12: Containers for randomisation code 40 – Month 1-6 shown – pre-labelled by production pharmacy to maintain the blind.

The Production pharmacy was sent the pre-specified randomisation codes by an independent Imperial Clinical Trials statistician. The study team remained blinded to these codes. The study team received 12 containers for each of the 60 randomisation codes (sent in 5 deliveries during the trial due to Ranbaxy Atorvastatin having a limited shelf-life). With each delivery, spares of statin and placebo were included. Trial medication was transported from the production pharmacy and stored in a temperature-controlled locked pharmacy room in the

Peart Rose Research Unit. The Hammersmith Hospital trials pharmacist was trained on the trial protocol and was also sent a copy of the randomisation list by the independent Imperial Clinical Trials statistician so that in the event of loss of medication the spares were available so a new supply could be labelled and dispensed by the Hospital trials pharmacist whilst ensuring the study team maintained the blinding. The study doctor wrote a prescription for trial medication using the randomisation confirmation. The study nurse then selected trial medication based on the pre-specified randomisation code (see prescription and photo of containers in Figure 12 and labels for the trial medication in Figure 13). The study doctor checked the trial medication prior to dispensing and then the study nurse and doctor confirmed the patient's identity and gave the trial medication to the participant. The participant was reminded at each monthly contact to keep hold of all containers and remaining tablets to return at end of trial and a pill count was undertaken. It was documented if participants lost or discarded containers. Figure 13 shows the blinded tablet and no treatment labels that were on the trial medication also known as the investigational medicinal product (IMP).

Guy's and St Thomas' NHS
NHS Foundation Trust
Guy's Pharmacy Manufacturing Unit

Investigational Medicinal Product Label Form

Trial: SAMSON
Chief Investigator: Prof Darrel Francis
Sponsor: Imperial College AHSC

Month ______ of 12
For use in trial, please take ONE tablet daily from this container from the 1st day until the last day of the month of: ______________

Atorvastatin 20mg film-coated tablets or PLACEBO
Directions: Take ONE tablet daily from this container for 1 month

Participant name: ______________

Randomisation Code	Participant ID no: ______________ Date of supply: ______________

Chief Investigator: Prof Darrel Francis. Sponsor: Imperial College AHSC
SAMSON Study EudraCT: XXXX-XXXXXX-XX
Peart-Rose Research Unit, Area C, 1st Floor, Hammersmith Hospital, Du Cane Road, London, W12 0HS. Tel: XXXX XXX XXXX

KEEP OUT OF REACH AND SIGHT OF CHILDREN : STORE BELOW 25C
BN: IMP116/XXX Expiry Date: XX XXX XXXX 31 tablets

Pharmacy, Guy's & St. Thomas' NHS Foundation Trust, London SE1 9RT. Tel: 0207 188 4992 MIA (IMP) 11387 ANS520

Month ______ of 12
For use in trial, from the 1st day until the last day of the month of: ______________ please take NO study treatment.

NO TREATMENT MONTH
Directions: Do not take any study treatment from the 1s tday until the last day of the month.

Participant name: ______________

Randomisation Code	Participant ID no: ______________ Date of supply: ______________

Chief Investigator: Prof Darrel Francis. Sponsor: Imperial College AHSC
SAMSON Study. EudraCT: XXXX-XXXXXX-XX
Peart-Rose Research Unit, Area C, 1st Floor, Hammersmith Hospital, Du Cane Road, London, W12 0HS. Tel: XXXX XXX XXXX

KEEP OUT OF REACH AND SIGHT OF CHILDREN : STORE BELOW 25C
BN: IMP116/XXX Expiry Date: XX XXX XXXX

Pharmacy, Guy's & St. Thomas' NHS Foundation Trust, London SE1 9RT. Tel: 0207 188 4992 MIA (IMP) 11387 ANS524

Figure 13: Investigational medicinal product labels for the blinded months (Atorvastatin 20mg or placebo) and unblinded months (no treatment months).

3.8 Manufacturing

During the setup of the trial, after researching quotes from NHS and private production pharmacies, the Guys and St Thomas's pharmacy were chosen for the manufacture of the trial medication. It was the only identified NHS production pharmacy that was able to create a matching placebo rather than over-encapsulating tablets. Other pharmacies were able to produce blister packs, which were deemed more like routine pill taking and better for adherence. However, it was considered more important to have tablets that matched and could not be picked apart as per over-encapsulation. The sponsor signed a contract with the production pharmacy. The original pharmacy quote was £30,639 excluding VAT. This included the set-up fee, which required the pharmacy to import a special template to design the placebo tablet, and generation of a simplified investigational medicinal product dossier (IMPD) for

the placebo and submission documentation for the Medicines and Healthcare products Regulatory Agency (MHRA). Ranbaxy tablets were used and repackaged in the containers. The fee included manufacture, pack-down and Qualified Person (QP) release under manufacturer's authorisation of investigational medicinal product (MIA(IMP)) 11387. 7440 active tablets and 7440 placebo tablets plus excess were packed into containers with child resistant closures and a silica gel desiccant in pack sizes of 31 tablets. 4 packing runs were originally scheduled of each active and placebo over the recruitment duration. A single batch of 240 labelled empty or 'no treatment' bottles were created at the start of manufacture and labelled differently to the active and placebo. Containers were labelled with annex 13-compliant labels and so complied with the requirements of the European Union directive 2003/94/EC. Each set consisted of 4 active, 4 placebo and 4 empty containers. Each set was assigned a specific code according to a randomisation list. Code-break envelopes were supplied for all 60 packs at the start of the trial. Medication was delivered by courier via temperature monitored delivery to the site and the study monitor verified at the end of the trial that no code break envelopes had been unsealed. The production cost of a 12-month supply of trial medication was approximately £510 per participant.

3.9 Schedule of visits

The participant started the trial on the 1st day of the next calendar month after the screening and randomisation visit unless that was the first day of the month in which case they started on the same day. On the first day of the trial the study nurse completed a telephone interview with participants confirming any adverse events or changes to medication and completed the monthly questionnaires. See Table 3, schedule of visits. All data for the trial was entered into the SAMSON trial database on InForm and monitored by the Imperial Clinical Trials monitor (see in Appendix 6 extract of monitoring plan showing routine monitoring).

Table 3: Schedule of SAMSON visits

	D1	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M18
	Screening & Enrolment visit	Telephone follow-up	Telephone follow-up	Telephone follow-up	Telephone follow-up	Telephone follow-up	Telephone follow-up	Telephone follow-up	Telephone follow-up	Telephone follow-up	Telephone follow-up	Telephone follow-up	End of Study Visit	6-month Follow-up visit
Informed consent	X													
Eligibility	X													
Demog.	X													
Medical history	X													
BP	X													
Lipid Profile (optional)	X													
Interview	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Euroqol	X	X	X	X	X	X	X	X	X	X	X	X	X	
TSQM	X	X	X	X	X	X	X	X	X	X	X	X	X	
CLE	X	X	X	X	X	X	X	X	X	X	X	X	X	

3.10 End of trial visit

After the Month 12 visit was completed, the study nurse performed 'scheduled unblinding' on InForm, which time stamped the date and time the unblinding occurred. The study nurse completed the scores for the 12-months and the randomisation code in a pre-designed spread sheet. The data manager also undertook a separate automated calculation and compared results to verify no errors in the calculations of the mean placebo, statin and no treatment scores. All participants received their results in the same graphical format (see example in Figure 14). The results also included a table of mean placebo, statin and no-treatment scores. The study doctor gave the results to participants in person at the same visits and a letter was sent to the participants' GP which included the results with recommendations based on the discussion with the participant. Feedback was also collected about the trial design and app during this visit.

During this visit, the nurse clarified medical history recorded at baseline was correct, current status of AEs and current concomitant medications being taken. Due to the emerging 19 pandemic in February 2020 all but one of the remaining end of study visits were conducted by telephone.

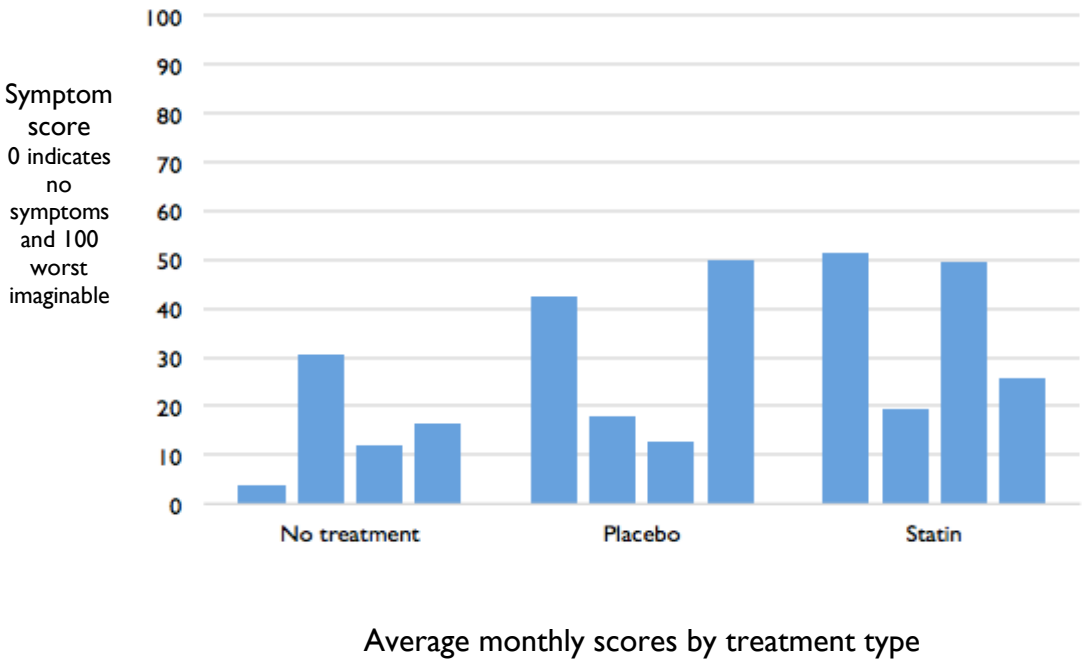


Figure 14: Example of graphical format participants received

3.11 End of trial + 6 months

6 months after the participant completed the trial, participants were contacted by telephone and asked:

- if they were now taking a statin or not
- the reason for any change in this decision
- how they now attributed prior side effects
- whether they considered the trial useful in understanding their side effects.

3.12 Data processing

The study nurse entered all data on InForm. The study doctor assigned principal investigator duties signed off SAEs and AEs. The chief investigator signed off all protocol deviations and protocol violations. A proportion of data was source verified by the study monitor as per the monitoring plan. All consent

forms and serious adverse events were source verified by the monitor. A data monitoring committee was also established, and they reviewed the trial safety data throughout the trial.

3.13 Outcomes

The pre-specified primary outcome was the ratio between the excess symptom intensity experienced by the placebo tablet, and the excess symptom intensity caused by the statin tablet.

The secondary outcome was number of participants restarting a statin 6-months after the end of the trial. Data collected at EOS+6-month visit.

3.14 Statistical analysis

A statistical analysis plan (SAP) was written by an independent trial statistician who remained blinded to the data (see SAP in Appendix 7). The statistical analysis and pre-study sample size/power calculations were performed by an independent statistician with expertise in scale development. Deviation from this SAP will be discussed as part of the results in chapter 5. For the purposes of rigour an independent statistician undertook the analysis of the primary and secondary outcomes.

3.15 Power calculation

For hypothesis 1, that hypothesised that of the patients enrolling for the study, 30% or more would complete the study. The intention was to report the proportion of patients completing the study and its 95% confidence interval. Based on the binomial principle, $SE_p = \sqrt{p \cdot q / n}$, the number of patients planned after the calculation below (50) would permit this proportion to be stated with a 95% confidence interval of $\pm 1.96\sqrt{\frac{1}{2} \cdot \frac{1}{2} / 50}$. Thus, the proportion was planned to be reported with a margin of error of ±14% or smaller. If the long-run proportion of patients who finished the study was ~70%, then a sample size of 50 would give 85% power to detect this at the 5% significance level.

For hypothesis 2 that more than half of side effects of statins would be non-pharmacological. Each “nocebo proportion” would be a value, which, for the sake of this calculation, was assumed to be between 0 and 1. It was planned

to report an average nocebo proportion for the population that has a 95% confidence interval of ±10%. To achieve this, assuming a worst-case scenario of individual-patient values scattered uniformly from 0 to 1 (i.e., SD = 1/√12 = 0.29) it was required the number of patients studied to be ≥n where 0.29/√n ≤0.10/1.96, i.e., n>(1.96×0.29/0.10)^2=36.

It was therefore planned to recruit 50 participants.

It was assumed the calculated nocebo proportion would likely be a fairly large fraction of 1 and occasionally greater than 1; and it was assumed it was unlikely to be less than 0; therefore, this calculation was deemed conservative.

The statistical properties of ratios of measurements are non-linear, so necessarily some simplifications in these power calculations are made. Firstly, it was assumed that the active tablet arm has substantial side effects. Individual patients represented this severity with different absolute numerical magnitudes, so for this power calculation it was define as:

A_1, A_2, A_3 … A_{112} as the 4×28 daily severity scores on active treatment

N_1 … N_{112} as the 4×28 daily severity scores on nocebo

Z_1 … Z_{112} as the 4×28 daily severity scores on no medication (zero tablets)

The averages of these respective data were m_A, m_N and m_Z, and their standard deviations s_A, s_N, s_Z.

The formula $(m_N-m_Z)/(m_A-m_Z)$ for the nocebo ratio, and its standard error assumed as long as m_Z was small compared to m_A and m_N, and s_A was not large in relation to m_A, it was a reasonable approximation to the fractional standard error of the nocebo fraction $(m_N-m_Z)/(m_A-m_Z)$ is $(s_A/m_A + s_N/m_N)/\sqrt{112}$. Real-life months are mostly slightly longer than 28 days, so the actual standard error was expected to be very slightly smaller. It was expected symptoms would be relatively high on tablets (whichever type), i.e., the A and N values would not be scattered over the full spectrum but clustered at the upper range for that patient. Thus sA/mA and sN/mN would each be of the order of ~0.2. The

standard error of the nocebo ratio would therefore be 0.037, i.e., the nocebo ratio, a percentage, could be given with a 95% margin of error of ±7 percentage points. However, the data monitoring committee considered it too complicated for interpretation to provide participants /layperson with confidence intervals in their individual results, so these were omitted.

3.16 Ethical Considerations

The trial was reviewed and approved by the Brent Research Ethics committee, see approval letter in Appendix 8. See Appendix 9 for dates of all regulatory and ethical approvals. The Imperial Trials Unit Quality Assurance Manager assessed the trial for risk. The trial was rated as 'Low-Risk of Harm' and it was determined the potential of the trial to reduce mortality and morbidity by helping participants determine if statins are the cause of adverse symptoms was clearly justifiable. There was no deception involved in this trial, participants were informed that the trial medication would be blinded. There is a risk that the trial could have been stressful or exacerbate mental health problems and hence eligibility excluded those with serious mental health issues. Also, there is a risk of harm to the baby if a woman is pregnant or breastfeeding when taking statins, so women of childbearing age who were not on a suitable form of contraception or had been through the menopause less than 1 year ago were not eligible. Participants were asked for feedback at the end of their study participation and if they withdrew the reason for withdrawal was elicited to determine if there was any other unforeseen distress caused by the trial.

3.17 Recruitment strategies

As the SAMSON involved inviting patients to restart a drug that they perceived had previously harmed them, the research team anticipated a high rate of refusal. It was expected that the exclusion of participants who took >2 weeks to develop symptoms might lead to a high number of pre-screening exclusions.

GP practices in North West and South West London were initially one of the main invitation routes. GPs were too busy to identify and invite patients face-to-face so instead database searches were conducted, and letters sent out to possibly eligible participants. This was coordinated by the GP Federation. The

letters of invitation enclosed an information sheet, a questionnaire and a freepost envelope. One identified issue with database searches was that there was not usually a specific code within the practice database for ‘statin intolerance’, so searches sought patients who had a previous statin prescription which was no longer maintained. In terms of eligibility this led to many ineligible participants being invited. Due to the mode of invitation, it was not possible to determine how many of the non-responders were actually eligible. Within Imperial Healthcare NHS Trust (where the study centre was based) all cardiology related clinics and related services such as cardiac rehabilitation had posters about the trial placed in the waiting areas and the medical and nursing teams were sent regular reminders to identify eligible patients. In addition, all lipid clinics within approximately one-hours travel time from London were invited to participate and interested sites were set up as ‘patient identification centres’ (PIC). Facebook adverts through an internet search company were also trialled. However, many participants who responded were either not eligible or non-contactable. As study nurse, I spent a lot of time contacting potential participants. An amendment to the ethics committee was submitted to use pre-screening questions on the landing page for the Facebook adverts and this allowed more immediate determination of whether the people responding were eligible and interested. This mode of approach was discontinued, as few willing participants were actually identified as well as it being relatively expensive and time consuming. Participants who had completed other research studies within the National Heart and Lung Institute were identified and invited. Another study known as Statinwise which had a similar design but was only evaluating myalgia as a symptom also referred volunteers who were ineligible for their trial. The SAMSON team reciprocated with their ineligible patients who were interested in the Statinwise trial. Cardiology charities also advertised the trial. In December 2018 an article was published in the British Heart Foundation (BHF) ‘Heart Matters’ magazine and hundreds of readers responded to the article, the trial reached its recruitment target in a matter of days (and recruited an additional 10 participants over the target). Appendix 10 shows all amendments to the trial design and protocol.

3.18 My intellectual contribution to the protocol and analysis

As the PhD candidate I was involved:

- In submitting the BHF grant application and being the named research nurse.
- In researching and selecting the investigational medicinal product design using a manufactured tablet rather than an over-encapsulated format to avoid patients unblinding themself by opening the capsule.
- In designing the research protocol and I am listed as a study investigator. In the design of the trial: writing the protocol, defining the eligibility criteria and proposing the idea of monthly questionnaires to validate the app. I was also involved in the key decision to recruit participants whose prior symptoms arose within two weeks of starting statins to ensure confidence in true adverse symptoms being reported within the 1-month treatment period during the trial. I also proposed the inclusion criteria to include secondary prevention CVD participants who had stopped statins as well as primary prevention participants.
- In the creation of the hypotheses.
- In writing the informed consent and information sheets and source data verification data sheet sent to GPs and using these documents to liaise with public & patient involvement and to gain volunteer feedback for refinement of trial design before the start of the trial.
- In writing study withdrawal and unblinding procedures.
- In designing the monthly follow-up visits.
- In conducting all qualitative and cognitive interviews.
- In submitting the applications and annual reports to funder, sponsor, ethics committee and competent authority.
- In preliminary validation of the app and coding of the qualitative analysis. In analysing all the questionnaires scores and qualitative data as well as designing the topic guides for the interviews.
- As a member of the Imperial Trials Unit and undertaking the role of trial coordinator.
- In reporting all AEs.

- In designing and performing the data cleaning schedule; writing the data management plan and all standard operating procedures for the trial.
- In preparing reports for the data monitoring committee, undertaking all safety analysis for the reports approved by the statistician, and liaising with the statistician over the statistical analysis plan, the process for imputation and the final analysis.
- In performing the analysis of results that was given to participants at their end of trial visit.
- In the final analysis, which was undertaken by an independent statistician for the purposes of rigour.

3.19 Summary of chapter

The trial method has been presented. The trial is a randomised placebo double-blind cross over trial, which includes randomised unblinded no-treatment periods. The trial was overseen by a clinical trials unit with experts in trial methodology. The trial was sponsored by Imperial College London and had approvals from NHS ethics and the MHRA. IMP for the trial had strict protocols for its management. Participants entering the trial had a baseline call and 12 monthly contacts with the study team after each month of the trial followed by an end of study (EOS) visit and an EOS +6-month call. All data for the trial was entered on a data capture system and integrity of data was monitored by the clinical trials unit. The trials unit also monitored adherence to the trial protocol. The recruitment strategies have been listed. My intellectual contribution to this work has been made explicit.

4 The SAMSON trial phone application development, testing and user feedback

The Self-Assessment Method for statin Side-effects Or Nocebo (SAMSON) trial used a phone application to collect symptom scores from participants. Symptom scores are used in the statistical analysis to calculate the primary endpoint for the trial. Therefore, the successful delivery of the trial depended on the application being a reliable and valid instrument for data collection. This chapter will start by outlining the key specifications required for the SAMSON trial application (app). The chapter then outlines the testing of these specifications and the application's performance. In addition, user feedback collected at various stages of the app's development is presented: first, the initial user testing of the app among healthy volunteers that led to the final app interface which was used in the SAMSON trial; second, testing the application using formal test scripts; third, cognitive interviews about the app with patients (who were not involved in the trial) but who had previously or currently taken statins; fourth, reported issues with the application during the trial and lastly end of study feedback from all trial participants about the apps performance during the trial. This chapter concludes by summarising the evidence that the app is a reliable and valid instrument and provides minor recommendations for its future enhancement and standardisation.

4.0 Background

The widespread use of mobile phones and access to the Internet has meant technology delivered components of health have increased in recent decades. In healthcare, technology-delivered components have been used for prevention, monitoring and risk assessment of medical conditions (Marcolino et al. 2018). In the SAMSON trial the technology delivered component was a telephone application that was used to monitor adverse symptoms; an overview of system specifications is listed below.

4.1 SAMSON system specifications

The SAMSON trial protocol required the recording of trial participants' perceived side effects or wellness/sickness associated with statin symptoms during their monthly treatment arms in preparation for the grant submission

the trial team identified key system specifications required for such an application:

A. Symptom scoring

B. Daily ratings

C. ‘Real-time’ data capture

D. Easy to use including users naïve to smartphones

E. Quick to score

The system fundamentally needed to be able to record symptoms (A. Symptom scoring). It was considered most useful for participants to rate their own symptoms on a daily basis and for these scores to then to be aggregated to a monthly score rather than have participants attempt to recall at the end of the month an average overall score for the entire month (B. Daily ratings). A single end of the month measurement was ruled out because it could be biased towards the latter part of the month, whereas daily measurement for the whole month was considered to be more reliable and would provide the opportunity for further subsidiary analysis such as assessment of the pattern of side effect presentation, including delayed side effect manifestation. Furthermore, for safety purposes the study team needed to monitor scores more frequently than just the end of the month and it was deemed a valuable specification of the app that scores could be captured in ‘real time’ (C. ‘Real-time’ data capture). Monitoring scores daily through ‘real time’ capturing of data was important to ensure participants were adhering to the study protocol and for safety purposes in case high levels of side effects occurred during the trial. Therefore, a phone application was considered to be the most suitable way to capture this type of daily measurement because it is a portable device that participants could transport with them, and it uses mobile data or WIFI to upload scores back to the server and reach the research team in a timely manner. The study team considered, in this first trial, it was important that participants should not be able to monitor their previous scores on the app, as this could itself change their behaviour and interfere with the interpretation of their results.

The app needed to be easy-to-use including for people who were inexperienced with using mobile phones. Hence, it was important to ensure that ‘smartphone naïve’ participants could be trained on how to use the app within a short space of time and then successfully score using the app. Therefore, preliminary user

testing of its simplicity to use was important (D. Easy to use including users naïve to smartphones).

For each participant entering the trial, the screening visit identified symptoms previously experienced with statins and that were to be monitored daily as they were so severe that they previously caused cessation of statins. Also, all symptoms were planned to be recorded at the end of each monthly visit. Therefore, this information was planned to be explored and captured systematically during the screening visit and monthly visits, so it was not necessary to explore symptomatology qualitatively on the app, but instead the requirement was to quickly and accurately quantify total level of overall symptoms experienced.

A quantitative visual analogue scale was chosen as the measurement tool on the app because this type of response scale has previously been shown to be valid in measuring constructs such as symptomology and health related quality of life and has been reported to be easy to use by participants in previous trials (Sung and Wu 2018, Shmueli 2005, Klimek et al. 2017, Hawker et al. 2011). Furthermore, a continuous measure was required for the statistical analysis in order to calculate the means (see chapter 5). With the intention to keep the app as simple as possible, it was considered most suitable to score overall symptoms or side effects on a singular measure; firstly, because symptom identification is less relevant to stopping a drug then overall symptom burden and secondly it kept the app as simple as possible in order to reduce the time taken to score/user burden (E. Quick to score).

4.2 Development of the SAMSON application

James Howard and Matthew Shun-Shin, who are study team members developed the app with no external funding.

The development of the application used an Iterative model of software development which gains better iterations of the software, as opposed to a more traditional step-by-step design process (Wirfs-Brock and McKean 2002). This approach to software development was advantageous because resources for the application development were limited and pre-dated the grant award. This type of approach also allowed the software to be easily adapted. The application incorporated the fundamental requirements for which the designers

then found software solutions. Software was coded, integrated, tested and evaluated. Use of the software provided further understanding about other key specifications required for the app.

It is beyond the scope of this thesis to go into the specific details of the technical development of the app, but Appendix 11 gives 'the SAMSON Phone Scores User Requirement Specification' document which describes how the application works including the programmes and operating information the application uses as well as how it adheres to data security requirements. See Figure 15 for a diagram of development and testing of the application. The first version of the app underwent user testing with healthy volunteers.

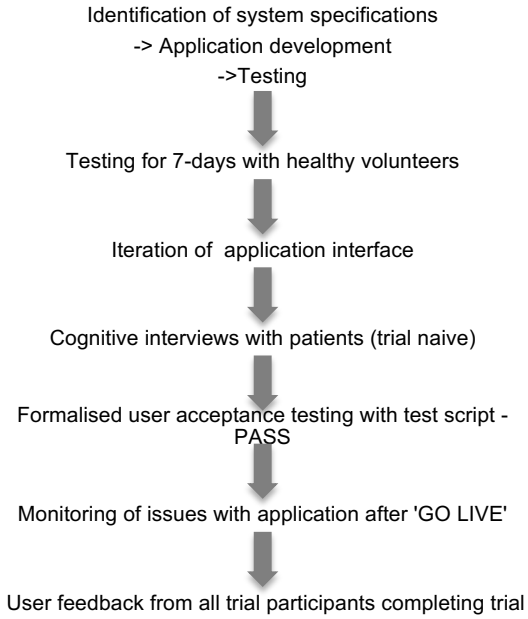


Figure 15: Stages of development and testing of the SAMSON phone application

4.3 Feedback from healthy participants trialing daily visual analogue score

4.3.0 Aims

To verify acceptability of the phone application among healthy volunteers and to confirm that the key specifications of the app were fulfilled.

4.3.1 Method

The application was trialled for one week among healthy volunteers. Volunteers had no existing cardiovascular diagnosis and were on no regular medication. As well as the application, volunteers also had to complete daily the visual analogue scale on paper of the EQ-5D-3L scoring system not the scale itself

(Devlin and Brooks, R. 2017). Use of this additional scale was to preliminarily validate the apps interval rating scale against a well-established one. As volunteers were not on any medication, rather than ask volunteers to score in terms of side effects on the app and the EQ-5D-3L, they were required to report how cold or warm they felt in the past 24-hours, on both of the visual analogue scales. At the end of the 7-days of scoring, participants were asked to complete a short questionnaire to determine if the participants viewed the specifications of the phone application to have been met.

4.3.2 Results

16 healthy volunteers (all members of staff in the researcher's department), mean age 37 ± 11.7 years old, completed both scoring systems on a daily basis for 1-week. The responses and individual correlations for each volunteer are shown in Figure 16. The application showed good agreement with the EQ-5D-3L sample standard deviation (SDD between 0.4 and 17.5). R^2 for the pooled results was 0.86.

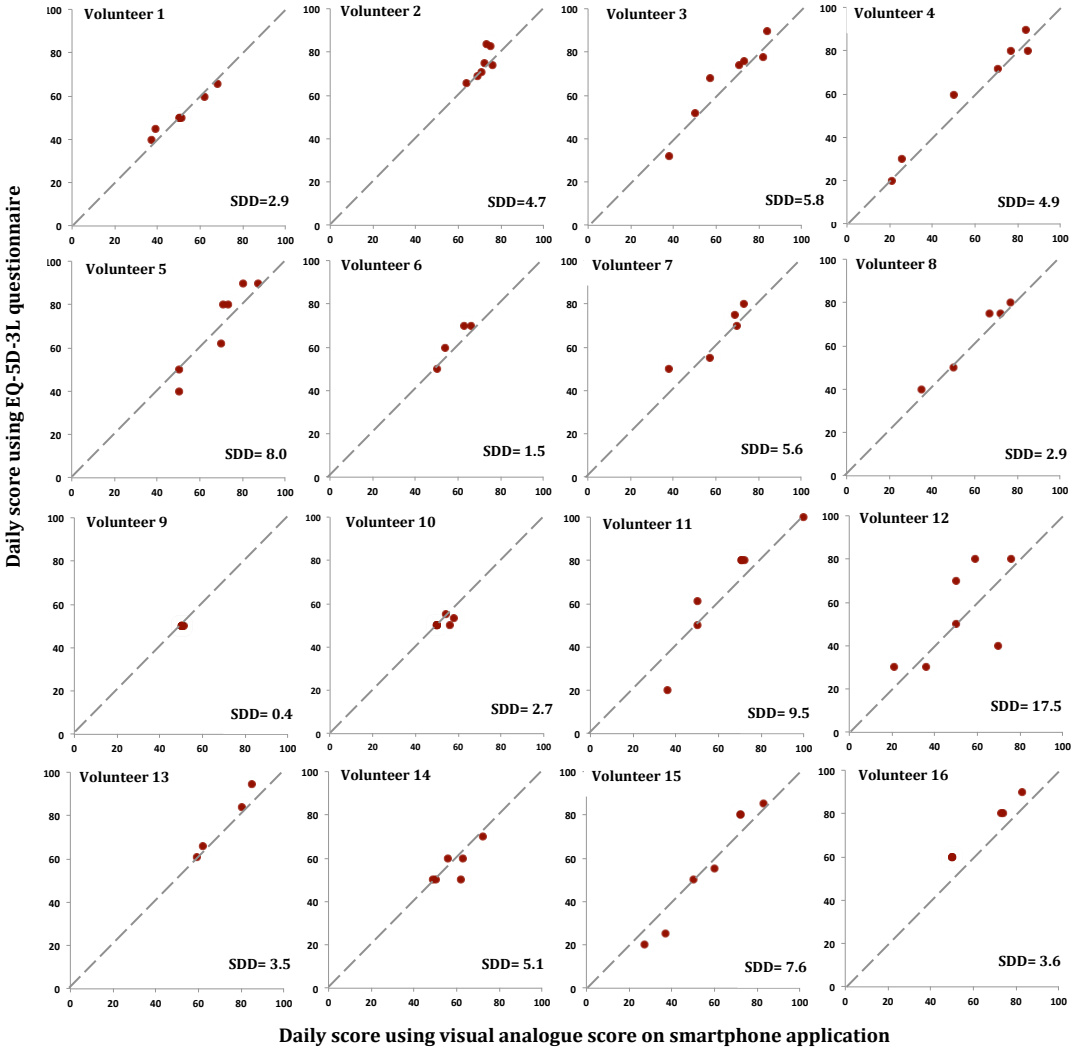


Figure 16: Individual graphs displaying the correlation between my digital visual analogue scale and the paper visual analogue scale used in EQ-5D-3L.

4.3.3 Feedback from healthy volunteers

See Figure 17 for responses to the questionnaire about the usability of the application and Figure 18 for open-ended spontaneous feedback grouped by theme.

1. Speed of completion: How long did it take you to use the application each day?

<30 seconds	30 seconds-1 min	1-2 minutes	2-5 minutes	>5 minutes
11	4	1	0	0

2. Ease of use: How easy to use did you find the application?

Very easy	Easy	Medium	Hard	Impossible to use on a daily basis
11	4	1	0	0

3. Ease of rating: How easy did you find the response scale on the smartphone to use to rate how hot/cold you felt?

Very easy	Easy	Medium	Hard	Impossible to use on a daily basis
12	3	1	0	0

Figure 17: Volunteers responses to survey about the phone applications usability at the end of trialling phone application.

Ease of use:

"Easy to use app, took <30 seconds on each day. No concerns- would be easy to use on a daily basis"

Difficulty with use:

"I am technologically savvy, I feel someone less technologically able, who has not used a touch screen-like device before may struggle. I therefore, think instructions with picture like diagrams would be helpful."

Forgetting to score:

"Forgot to record my responses over the weekend as not used to having 2 phones. Perhaps having the app as part of my regular phone would have improved/aided my memory."

"The system was easy to operate, unfortunately I struggled to remember to monitor every day. I didn't use the reminder service which would have helped."

Figure 18: Spontaneous comments to survey by volunteers about the phone applications usability grouped by theme at the end of trialling the phone application for 7-days.

4.3.4 Discussion and Conclusion

Initial user testing was extremely positive; no volunteers took longer than 2-minutes per day to score on the application and the majority of volunteers rated

the application in under 30 seconds. None of the volunteers considered the app or rating of the app difficult. It was suggested people who were less ‘technically savvy’ might require more instructions to use. One user found it difficult to remember to score every day but had not used the in-built reminder service.

4.4 Iteration of app following volunteer feedback

Following user testing, the app was further modified, see Figure 19 to see the modified interface. The in-built reminder service was removed from the app due to compatibility issues. However, as all smartphones have the capability of setting reminder notifications it was planned to instead recommend to participants to set a reminder on their phone and if a participant did not score regularly during the trial to again reiterate this function.

Figure 19a. Welcome menu, indicating trial progress and the current designated container of medication.

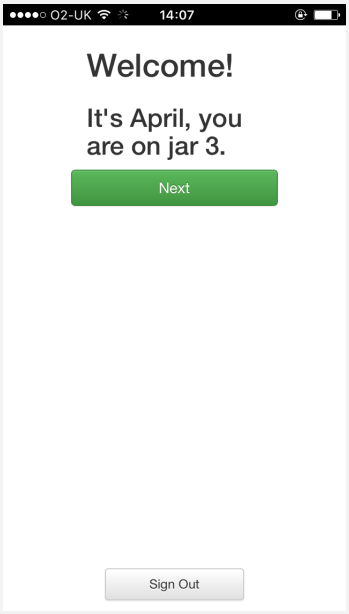


Figure 19b. Touch-screen selection of tablet compliance.

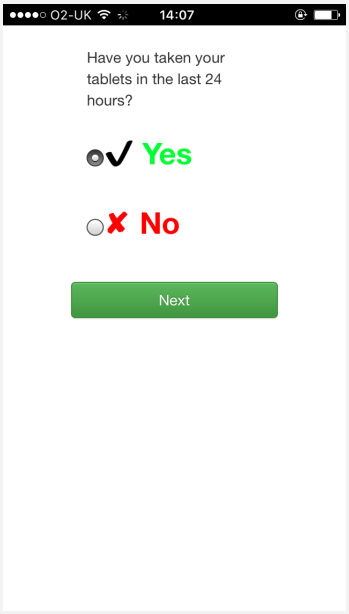


Figure 19c. Visual analogue scale using touch-sensitive slider to score symptoms.

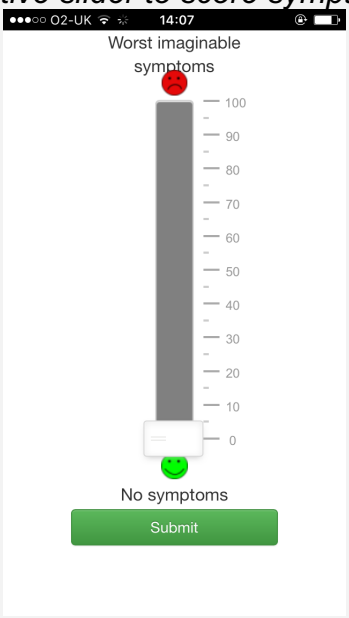


Figure 19d. Exit menu and touch-screen selection to score again

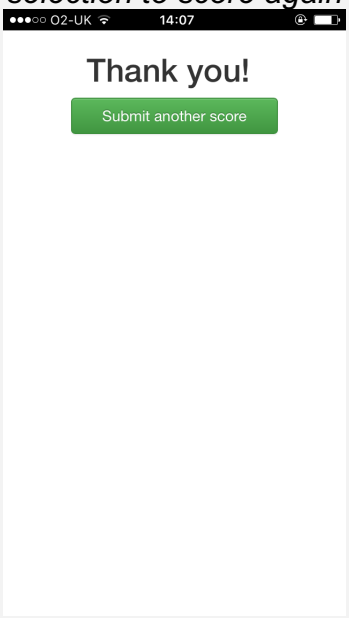


Figure 19: a-d: Screenshots of the application interface, in the order they appear to trial participants scoring on the phone application.

4.5 Regulatory requirements of application

A computerised system supporting good clinical practice must confirm the system operates to the stated requirements and latterly be General Data Protection Regulation (GPDR) compliant. See Appendix 12 summary of the

user acceptance testing which shows the phone application passed all tests using test scripts prior to ‘Go Live’. As part of the initial iteration of the application, the name of the user was removed from the welcome screen and replaced with a generic message. Personalisation was balanced against the benefits of confidentiality and by removing the name, it allowed data collected to be completely pseudo-anonymised and linked only by an identification number.

4.6 Application validation

A valid measure is a measure that truly measures what it is supposed to measure (Robinson 2017, Peter 1979). Validity is measured in various different ways. Firstly, face validity is used to determine if people perceive the scale to measure what it purports to measure and that participants understand what the scale is asking them to rate. Secondly, construct validity assesses if the scale measures the construct it is intended to measure. Thirdly, criterion validity assesses if the scale corresponds with different tests or criterion measures. Lastly, the content is fully representative of what it aims to measure. Unreliable measures reduce the validity of the findings of research because of measurement error. Good reliability of a measure can be determined by high correlation between repeat measurement (test-retest) when the underlying condition is unchanged. High correlation between repeated measures indicate less error (Robinson, M. A. 2017, Peter 1979).

The four types of validity have been explored. Reliability of the scale requires each repeated measurement under the same conditions to give the same score, the conditions in the trial means variation might be expected and might actually reflect the construct under investigation, not error. Therefore, a separate study would be required to perform detailed reliability checks.

Face or surface validity were established through the pilot questionnaire which also has the dual purpose of checking scales are manageable and asking the right questions. Construct validity can be measured by correlating with existing side effect questionnaires and by comparing correlation with side effect and quality of life questionnaires.

This thesis introduces a very preliminary assessment of validation. Future

investigation of the application would need undertaking to look at ecological validation which is whether the results are the same outside of a clinical trial context.

4.7 Cognitive interviews

4.7.0 Introduction

The SAMSON trial relies on trial participants completing daily symptom scores and monthly questionnaires. People's score can be influenced in unintended ways by the wording of questions, by the ordering of items and by the type of response format (Morgado et al. 2017). Cognitive interviews can determine comprehension of the questionnaires by respondents, provide insight into how people retrieve or recall information for answers and give insight on judgment and response choices.

4.7.1 Method

As part of the interviews reported in chapter six, cognitive interviews were conducted with participants who were identified when they either declined participation in the trial or were not eligible for it but who were willing to discuss their experience of statins. Therefore, participants were SAMSON trial-naïve participants. The cognitive interview was conducted following open-ended questions asked about patients' experience of statins (reported in Chapter 6).

The SAMSON phone application and the monthly questionnaires were examined in more detail through cognitive interviews, which asked probing questions about the scales that were used in the SAMSON trial. See Figure 20 for the topic guide used in the cognitive interviews. For the EQ-5D-3L and Treatment Satisfaction Questionnaire for Medication (TSQM 1.4) probing questions were used to determine a participant's experience of completing them. As these two questionnaires were already well-validated scales and their license of use did not allow editing them, questioning was briefer and more to determine if the questionnaire was seen to be appropriate by participants. Participants were asked to speak aloud if they felt comfortable while filling out the paper questionnaires (EQ-5D-3L, TSQM and CLE) and the app to gain further insight into participants comprehension when completing questionnaires and to give the interviewer more information from which to probe further questions. After completing the questionnaires participants were asked probing

questions to understand what they understood by the questions and instructions for each scale including the app and their views of the response format.

Phone application

- What does the word 'symptoms' mean to you?
- Can you repeat the question 'Can you rate your symptoms today' in your own words?
- What were you thinking about when you answered the question?
- Was it easy or hard for you to answer the question?
- Was your answer among the response choices?
- Do you think it would be hard or easy for other people to answer that question?

EQ-5D

- Was it easy or hard for you to answer this questionnaire?

Treatment Satisfaction Questionnaire

- Was it easy or hard for you to answer this questionnaire?

Confounding Life Events Questionnaire

- Was it easy or hard for you to answer the questionnaire?
- For each question, was your answer among the response choices?
- How well do you remember events over the last month?

Figure 20: Topic Guide for cognitive interviews

4.7.2 Analysis

As described in chapter 6, this was an ethically approved sub-study, interviews were transcribed verbatim. I used NVivo Version 12.0 analysis software to organise transcripts and performed a content analysis (Weber 1990) on the data using the topic guide as the organising framework and thematically analysing any spontaneous or new themes arising from the interviews.

4.7.3 Results

15 of the 19 interviewed participants who took part in qualitative interviews also took part in the second part of the cognitive interviews (see chapter 6), 2 of the 4 who did not participate had declined as they wanted to discuss experiences of statins but were not interested to be involved in the cognitive interviews which was the second part of the interview. The other 2 interview participants cognitive interviews were abandoned due to poor phone line quality.

See Appendix 13 for EQ-5D-3L scale and alongside the results of the cognitive interviews. The majority of participants said they had found the EQ-5D-3L easy

to complete. One participant felt that the response choices were limited, she had to have assistance to wash her hair to avoid her ears getting wet and so she felt she would be forced to rate question 1 as having problems with washing and dressing when she felt in reality it was a relatively minor issue that she had. See Appendix 14 for TSQM. The majority of participants said that they found the TSQM questionnaire easy to complete, and several participants said they liked the seven option response choices. One participant highlighted that question 2 was not relevant as statins do not relieve symptoms.

See Appendix 15 for the CLE questionnaire. The majority found this questionnaire easy to complete. However, several participants suggested that the questions (questions 2, 3 and 5) about social and mental health issues might be upsetting. One participant stated as question 7 was about holidays, question 8 about change in routine should state that change in routine did not also include holidays. Also, one participant said question 7 regards 'holidays or time off for relaxation' should be quantified, as it was difficult to know if the amount of relaxation encountered within a given month reached the threshold amount to respond 'yes' to this question. The CLE during the trial was completed once a month, most participants stated they felt they could sufficiently recall events in the previous month to rate this questionnaire accurately. One participant felt that the older the person who was completing it, the harder it might be to recall information from the previous month. The majority of participants found the response choice acceptable, but it was discussed that if a person had many of the negative events in the questionnaire a binary 'yes'/'no' response may not be the most suitable and a more nuanced response choice format might be better. One participant suggested a binary response might deter some participants rating 'yes' to a negative question, as they may not want to make the leap in acknowledging it as a problem.

See Appendix 16 for the phone application. The majority of participants said the daily app was easy to rate, but one person said their consistency in scoring in the same way every day might be a problem. Another participant suggested scoring once a day limited their ability to change the score if their symptoms increased or decreased during the course of the day. Another participant was unsure of the cause of their symptoms and another participant thought that different people would rate the same symptoms at different intensities. The

response scale was deemed to be acceptable by the majority interviewed. One respondent suggested that it would be better to have qualitative descriptions of ratings or words next to the scale to assist people to rate in the same way and also to help people that found percentages difficult, also one person felt rating out of 10 rather than 100 was simpler. The comprehension or understanding of what 'symptoms' meant in the context of the app and 'can you rate your symptoms' was broadly equivalent across participants and seemed to have been comprehended by the participants in the manner intended. Figure 21 shows the spider diagram of what symptoms meant to each participant.

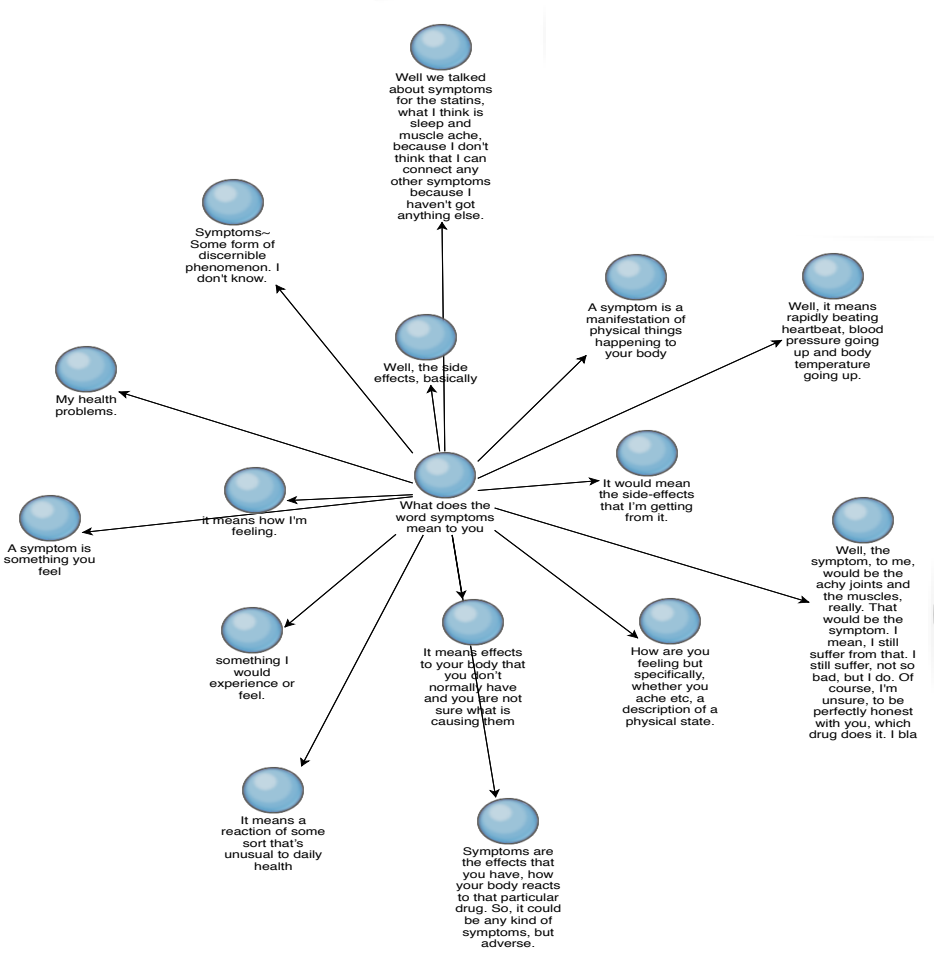


Figure 21: Spider diagram describing what the word 'symptoms' means to participants

4.7.4 Conclusion and Discussion

The majority of participants considered the scales as being easy to complete and suitable for use in the SAMSON trial. Not being able to change scores during the same day was suggested as a potential issue with the app. However, this is something that actually would not be a relevant issue for actual trial participants because the trial participants were instructed, they could score as many times a day and importantly if scores were updated the last score of the day counted, what is more participants were cautioned not to update score if their symptoms improved during the day as it would underrepresent their symptoms for that day. It was important to capture their worse experience each day even if short lived.

Another participant in the interviews raised the issue of being unclear about the cause of their symptoms. However, in essence this is the problem the trial hopes to address and, in the instructions, to trial participants they were instructed to score including on 'no treatment' months symptoms they previously associated with statins or any new symptoms they attributed to statins. Further to these issues, some participants raised the point that they were unsure if they would score the same way each day and another participant felt scores between participants would be very different. However, importantly the cognitive interviews have demonstrated the construct being measured is understood but some participants could struggle with a 100-point scale and might find qualitative wording along the interval scale helpful particularly to guide participants to rate in the same way. This was not changed for the trial but is something useful to consider for future versions of the app.

It was identified that the 'Effective dimensions of the Treatment Satisfaction Questionnaire for Medication (TSQM) was not ideal for statins, as statins do not provide symptom relief. Cognitive interview questions were designed to elicit discussion about the suitability of the questionnaire. Measurement invariance of the new app is whether it is interpreted/understood in the same way by participants whenever it is implemented, this was explored as a series of questions asked about the comprehension of symptoms and it appears it was understood or interpreted in similar ways by the different participants interviewed.

A limitation of the topic guide was that participants were not explicitly asked

about face validity; it may have been useful to ask participants directly if they felt that the scale measured what it was purported to measure. However, more broad and open-ended questions were used, which would have elicited spontaneous discussion about poor face validity if it was an issue. For a scale to be acceptable it should be relevant and meaningful, with clear meaning that is not ambiguous and easy to answer (Connell et al. 2018). The app appeared to be interpreted in the same way by different participants.

Cognitive interviews have limitations and are subjective, they have the potential to miss important issues particularly if not all groups are represented. This study had no defined sample size, also not everyone is comfortable talking about their experiences and views and so recruitment to interviews (see chapter Six) may have been biased towards people with certain traits e.g., extroverted personality types who may have been more willing to take part and share their views. However, undertaking a small number of interviews allowed the researchers to identify that in a sample of different people there was a general consensus or put another way they could understand in the same way what they were being asked to rate and there were no great issues with any of the measures used.

4.8 Performance of the application during the trial

During the trial (see Chapter Five), participants were encouraged even out of hours to report to the trial team all issues with the telephone application as soon as possible. Over the course of the trial, there were 9 malfunctions of the app recorded and 7 user issues. All 9 malfunctions related to an issue over the May 2017 Bank Holiday when an automatic update on the app led to all participants' apps not being able to send scores. Participants had to reinstall the app and log back in and a few days of data was lost on the first few days of May 2017. This data loss was reported as a protocol violation to the Sponsor. Some patients found it difficult to log back in after this incident, the main issue being, that they were unfamiliar with the underscore "_" key and unable to locate this button on their smartphone, which is a standard character in all username formats. Auto-updates are now permanently switched off and the underscore will be removed from usernames in future trials.

Another issue with the app was finger dexterity and one participant kept

accidentally logging out of the app. Therefore, the logout button was moved lower on the screen, and no further issues with logout arose. The remaining issues with the application during the trial were caused when participants did not have adequate phone signal or WIFI. In these instances, scores were not sent from the phone even once they had signal or WIFI again. The participants were alerted by myself that the trial team had not received phone scores from them for a few days and when they confirmed they had been scoring I advised the solution was to keep the application open for a few minutes after scoring to ensure the scores were then received. Data that had previously not sent were received.

4.9 End of trial participant user feedback

4.9.0 Aims

Trial participants using the application during the trial (see Table 4) were an important source of feedback about the application and provided insight about issues with the application that could be improved for its future use.

4.9.1 Method

Every trial participant who completed their end of trial visit was asked by the study nurse (FW) when no other trial team members were present, to provide feedback about the phone application. Participants were encouraged by the study nurse not to be concerned about giving negative feedback about the phone application or trial, as it would be helpful for improving the application in the future. The research nurse wrote all comments verbatim in their research notes and then transcribed them and content coded (Weber 1990).

4.9.2 Results

All participants completing End of study (EOS) visits (n=49) were asked for EOS feedback about the app with some participants who did not complete the trial this feedback was not collected as they did not undergo end of study visits, just an end of study +6-month visit. However, none of the participants who withdrew, stated their reason for withdrawal as being related to the phone application. See Table 4 for a summary of end of study feedback comments.

Table 4: EOS feedback from trial participants
✓positive feedback ✖negative feedback or recommendations

THEMES AND SUBTHEMES	FREQUENCY
APPLICATIONS PERFORMANCE	
✓ App satisfactory	31
✓ App easily transferred to new phone	1
✖ Previous score showing, had to log out and log back in to clear	1
✖ Date did not always change* *Isolated issue due use of an old phone – date correct on app	1
INTERVAL SCALE	
✓ Liked the directness of the question	1
✖ EQ-5D rating scale reverse of app so confusing	1
✖ Scoring symptoms of alopecia harder on the app	1
✖ Slider not precise	2
✖ Scoring 0 at bottom of scale rather than the middle feels wrong	1
✖ Scoring from 0 -100 subjective	1
✖ Questions the appropriateness of scoring from 0-100	1
✖ Interval scale in increments of 5 rather than 10 would be better	1
✖ Useful to be able to make notes on other tablets taken	1
✖ Guidance on scoring would be useful, what level appropriate	2
SCORING	
✖ Useful to score each symptom individually	1
✖ Difficulty recalling if had already scored	5
✖ A built-in reminder would be useful	5
✖ Useful to be able to see if had already scored that day	1
✖ Useful if app prompted to score	2
✖ Useful to describe symptoms qualitatively	1
✖ Useful to be able to see previous scores	2
✖ Signing out tricky if do not have the login details to hand	1

✖ Sometimes unsure if the score had gone through	1
✖ Submit another score should be 'revise or exit'	1
✖ App poor if designed by a professional company	1
✖ 'Have you taken trial medication' is an ambiguous question	1
✖ Issue with logging in	2
✓ Slider good	1
✖ 'On edge' remembering to score	1

4.9.3 Conclusion and Discussion

Feedback about the application was extremely positive with the majority of participants stating it was satisfactory. However, there were a lot of comments on ways to improve it. It was mentioned that it would have been useful to be able to see if the participant had given a score that day or not. However, the most recent iteration of the app used in subsequent trials, has an automatic reminder and prompts participants who have not responded in a given time frame.

4.10 TSQM Adjustment

In the cognitive interviews it was raised that the TSQM question about relief of symptoms was difficult to answer because statins do not actually relieve symptoms. Further to this, the user feedback from actual trial participants during monthly calls, again raised this issue but in regard to the whole 'effectiveness' domain of the TSQM, because the drug under investigation was a statin that does not normally elicit any beneficial effects apart from a lowered blood cholesterol which was not measured as part of the trial protocol. The 'convenience' domain also showed a 'ceiling effect' in that all participants regarded statins as an 'extremely easy' to take tablet. Finally, the 'global satisfaction' domain of the TSQM was also deemed to be difficult and almost nonsensical to answer in a blinded trial context. However, the side effect domain appeared very relevant and useful for preliminary validation of construct validity of the app. Therefore, the trial team sought permission from the trial's unit and the scale developer to use only the TSQM side effect domain. Scoring of all other domains ceased.

4.11 Preliminary validation of app

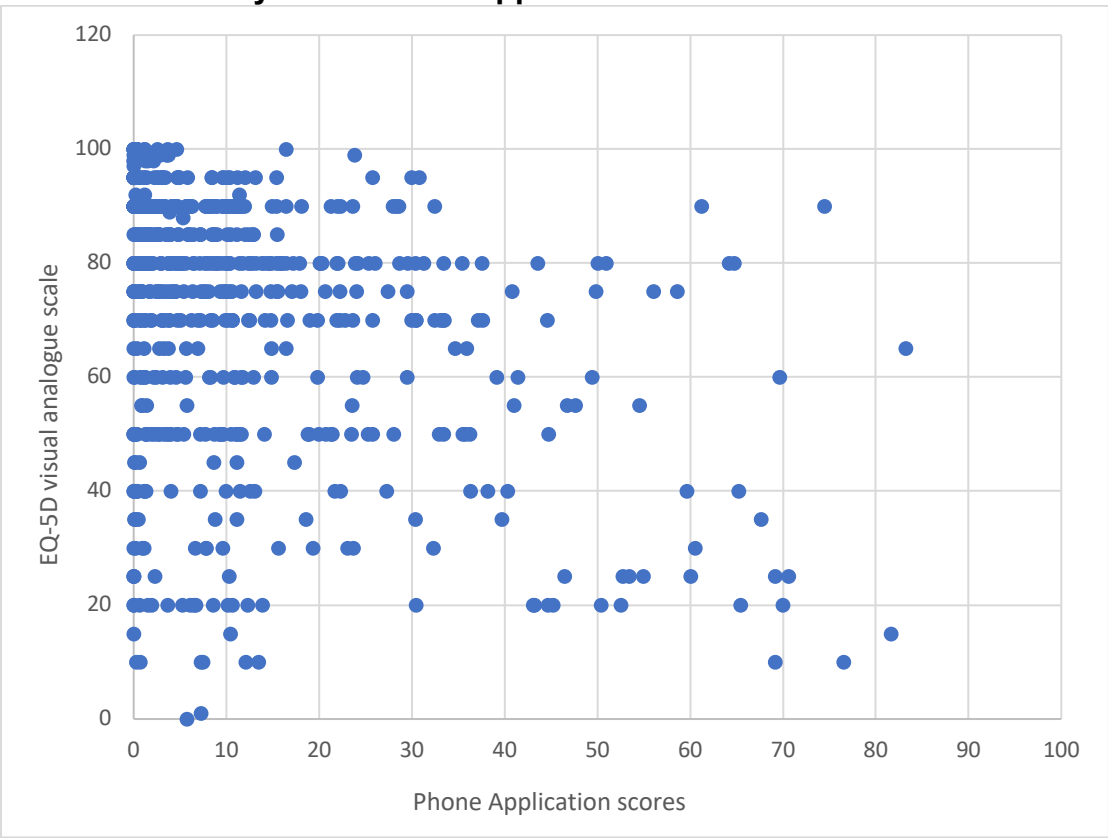


Figure 22: Scatterplot of mean monthly application scores plotted vs. monthly EQ-5D scores

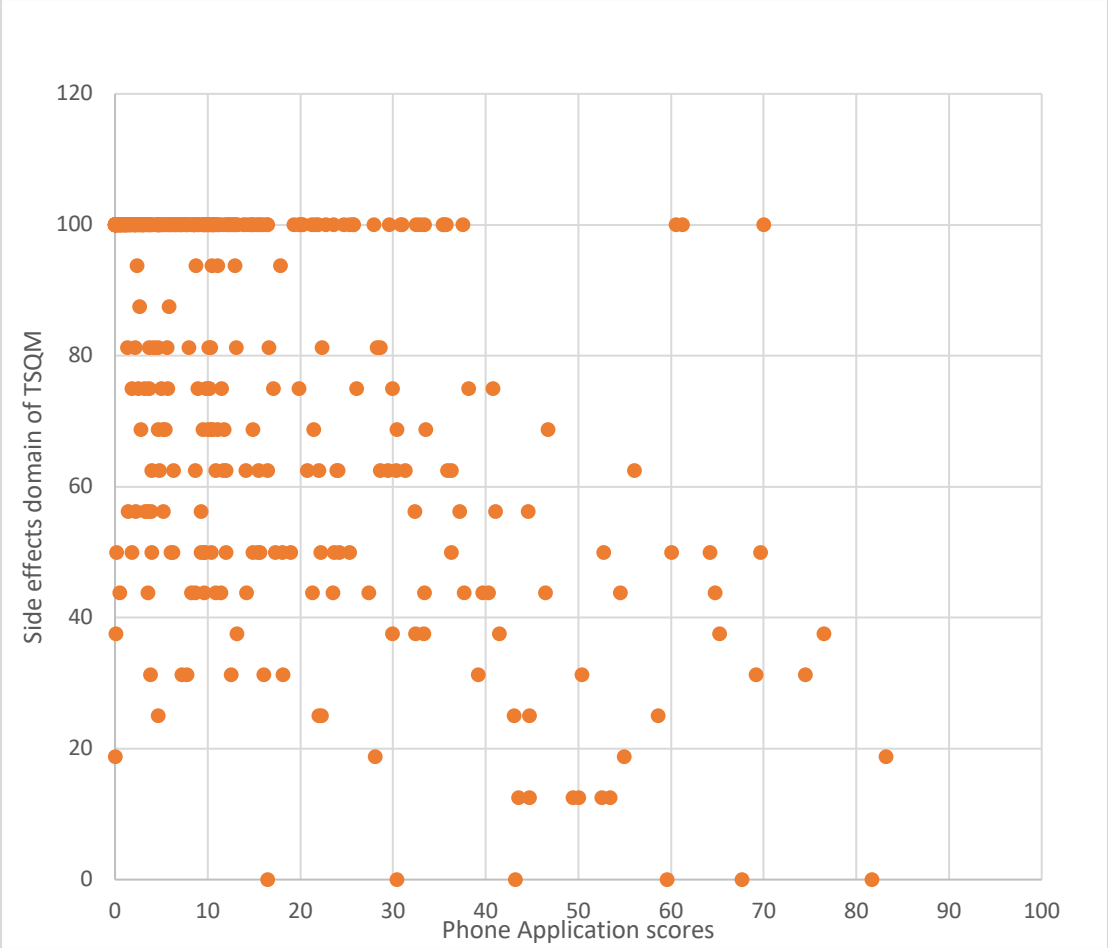


Figure 23: Scatterplot of application scores plotted against TSQM side effect domain scores

See scatterplots of the app vs EQ-5D interval scale. (Figure 22) and the side effects domain of the TSQM (Figure 23), both are well-validated measures of the constructs they purport to measure. As cases were related and the scatter plots showed the data was non-parametric a Spearman's rank correlation was then used to analyse correlation between measures. See Table 5 for app's correlation with the TSQM side effect domain and EQ-5D interval scale. The app negatively correlated with the EQ-5D interval scale with 0 on app denoting no symptoms and 100 indicating worst imaginable symptoms. Reversely, higher health state on the EQ-5D interval scale denotes better health state. The app also negatively correlated with the side effects domain of the TSQM; 0 on app denotes less symptoms. Conversely a low score on the side effect domain of the TSQM indicates more side effects. There was greater correlation (see Table 4) between the app and the side effects domain of the TSQM compared

to the app and the EQ-5D interval scale, which is reassuring because the app is intended to measure adverse symptoms more than general measures of quality of life.

Table 5: Spearman's rank correlation of SAMSON phone application vs. TSQM and EQ-5D

			SAMSON application	TSQM	EQ-5D
Spearman's rho	SAMSON application	Correlation coefficient	-	-0.536**	-0.311**
		Sig. (2-tailed)	-	0.000	0.000
		N	-	429	645
	TSQM	Correlation coefficient	-	-	0.320**
		Sig. (2-tailed)	-	-	0.000
		N	-	-	424

**Correlation is significant at the 0.01 level (2-tailed).

4.12 Future use of application and enhancement

As the results of the trial show (in chapter five) the application has potential use in clinical practice as a tool for determining if statins are the pharmacological cause of side effects. Another type of validation that has been found to be important is the 'NHS stamp of approval' which has been shown to be influential in health professionals recommending digital health solutions to patients. Published studies about the effectiveness of the technology were shown to be less influential to physicians than the NHS endorsement (Downey 2020).

Public Health England (https://www.gov.uk/government/publications/health-app-assessment-criteria/criteria-for-health-app-assessment) has provided criteria that apps used within the NHS should meet. It includes evidence of effectiveness, medical device regulation, clinical safety, security, privacy, regulatory approval, privacy, confidentiality, usability, accessibility and interoperability. The app shows promising signs of being able to meet all these criteria.

4.13 Conclusion and discussion

The app has been user tested prior to use in the trial. The phone application was considered by most trial participants as well as participants naïve to the trial to be easy to use. It is also a reliable measuring tool, with only one data loss episode. Some minor issues with the app were raised but these are considered something that could be modified in future iterations of the app.

Cognitive interviews showed that all the measures were seen as appropriate by trial participants. However, feedback from trial participants about the TSQM led to the adjustment to only use the side effects domain as the other domains were not considered applicable for a blinded trial or for statins.

4.13.0 Summary of results

Chapter four has presented evidence that the phone application is a valid tool for measuring symptoms in the trial. Firstly, users were able to understand instructions, use the app and score quickly each day. Secondly, the app correlated with well-established measures of treatment side effects and quality of life.

4.13.1 Interpretation of results

The results provide preliminary support of the app as a valid measuring tool.

4.13.2 Limitations of results

Further testing of the app is required within a large sample. Also, reliability needs to be tested, using a sample where test-retest reliability can be established.

4.13.3 Recommendations

In the UK the app does not just need to show scientifically it leads to better outcomes, to be recognised as a valid health app, NHS endorsement appears to be important for physicians to recommend such health care applications.

Now the applications development and testing has been explored, chapter five will present the SAMSON trial results.

5 Main trial results

5.0 Chapter overview

This chapter presents the SAMSON trial results. Sixty participants were randomised between May 2016 and March 2019. Forty-nine participants completed the full 12-month protocol. The mean symptom intensity was 6.3 out of 100 during no-tablet months (95% confidence interval 2.8 to 9.8), 12.1 during placebo months (8.6 to 15.6; $p<0.0005$ versus no-tablet months) and 12.8 during statin months (9.3 to 16.3; $p<0.0005$ versus no-tablet months; $p=0.499$ versus placebo months). The nocebo ratio was 0.90. 6-months after the end of the trial 50% of randomised participants had restarted a statin and were still taking it. Prior to the trial, side effects on statin tablets were severe enough to cause trial participants to abandon them but during the trial itself symptoms were predominantly due to the psychological rather than pharmacological effects of statin tablets. Side effects are found equivalently in placebo months and significantly less in open label no treatment months. Not only could the majority of participants tolerate the study protocol, but half of trial participants restarted a statin. Figures 27, 28, 29, 30, 31, in this chapter and Appendix 18 were coded using Matplotlib by Dr James Howard (Hunter 2007).

5.1 Recruitment

Recruitment took place between May 2016 and March 2019 (See Appendix 17 for recruitment by approach). The most successful recruitment strategies were self-referral (mainly through an article in the British Heart Foundation magazine) and clinician referrals from cardiology and lipid clinics.

5.2 Baseline Characteristics

Sixty-two individuals, who appeared eligible, attended for screening between 1st May 2016 and 1st March 2019. Sixty were eligible and randomised, see Figure 24 showing the consort diagram of participants through the trial.

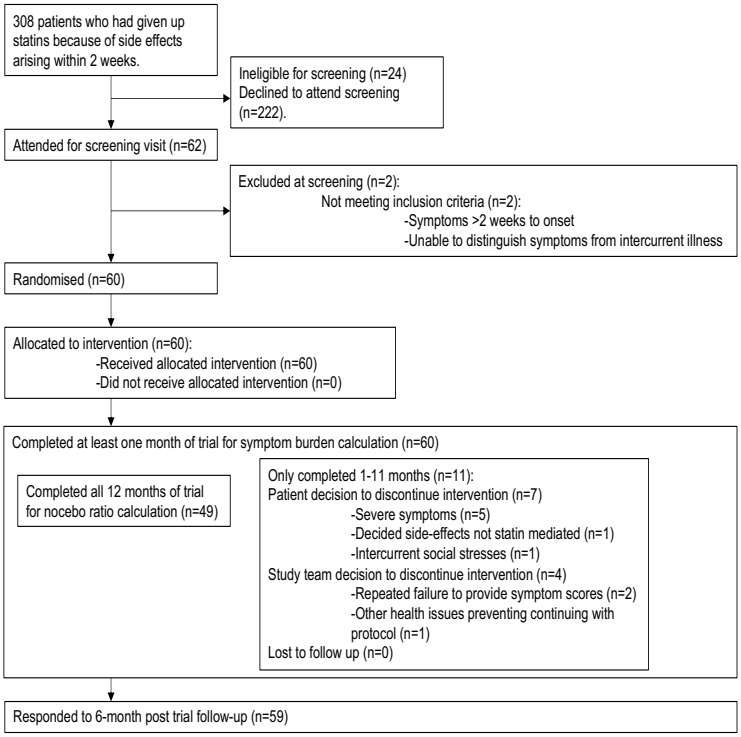


Figure 24: CONSORT diagram showing the flow of participants through the trial

Participants had previously tried a median of 2 statins each for a median duration of 1.1 years. In 46 participants (77%), the statin indication was primary prevention, (baseline characteristics are shown in Table 6).

Table 6: Baseline characteristics of the 60 randomised participants

Characteristic	Value
Age (years)	65.5 (8.6)
Gender	
Male	35 (58.3)
Female	25 (41.7)
Ethnicity	
White	54 (90.0)
Black	1 (1.7)
Asian	3 (5.0)
Mixed	2 (3.3)
Height (cm)	169 (8)
Weight (kg)	82.0 (19.0)
BMI	29.1 (6.7)
Number of statins previous tried	2 (2 to 3)*
1	13
2	24
3	11
4	7
5	5
Previous statin duration (years)	2.84 (4.65)
	1.06 (0.13 to 3.30)*
Systolic blood pressure (mmHg)	139.1 (17.3)
Diastolic blood pressure (mmHg)	77.5 (8.9)
LDL-C (mmol/L)	4.16 (1.07)
Current indication for statin	
Primary prevention	46 (76.7%)
Secondary prevention	14 (23.3%)
History of diabetes	4 (7%)
QRISK-2 (Hippisley-Cox et al. 2008) 10-year risk (primary prevention participants only)	24.3% (13.6)
Number of concomitant medications	4.72 (3.28)

*Continuous variables are listed as mean (standard deviation) unless otherwise indicated. Categorical variables are listed as count (percentage). * Median & inter-quartile range*

The commonest overall symptoms had been “muscle ache” (36 participants, 60%), “fatigue” or “tiredness” (9 participants, 15%) and “cramps” (6 participants, 10%). Twenty-seven (45%) attributed one symptom to statins at baseline and 33(55%) attributed more than one adverse symptom to statins at baseline. See Table 7 for frequency of adverse symptoms attributed to previous statins.

Table 7: Frequency of adverse symptoms attributed to statins prior to the trial

Adverse symptom at baseline	Frequency
Myalgia	36 (60%)
Fatigue	9 (15%)
Muscle Cramps	6 (10%)
Arthralgia	5 (8%)
Cognitive disruption	5(8%)
Nausea	4 (6%)
Mood disruption	4 (6%)
Aching	4 (6%)
Chest pain	3 (5%)
Skin tingling	3(5%)
Dizziness	2 (3%)
Rash and hypersensitivity reaction (not including anaphylaxis or angioedema)	2 (3%)
Back pain	2 (3%)
Diarrhoea,	2 (3%)
Vivid dreams	2 (3%)
Headache	2 (3%)
Acid reflux	2 (3%)
Nightmares	2 (3%)
Alopecia	1(2%)
Insomnia	1(2%)

Sensory disturbance other than visual	1(2%)
Vomiting	1(2%)
Malaise	1(2%)
Bloatedness	1
Loss of concentration	1
Kidney cyst	1
Nasal congestion	1
Dermatographism (hive like welts)	1
Head tenderness	1
Discomfort in calves	1
Weakness	2
Anxiety	1
Sleep disturbance	1
Crying	1
Eczema	1
Sore weepy eyes,	1
Eye dryness	1
Bone pain	1
Muscle tremor	1
Dry mouth	1
Gynecomastia	1
Muscle tightness	1
Bleeding at back of nose	1
Knuckle pain	1
Muscle weakness	1
'Upset' bowels	1
Knee pain	1

5.3 Withdrawals and loss to follow-up

Eleven randomised participants (full data in Appendix 18) did not complete the trial. Seven of these participants chose to withdraw from trial therapy: 5 because of severe symptoms (participants 1017, 1022, 1040, 1042 and 1054): Participant 1017 experienced trial fatigue and withdrew from the last two

months of treatment but continued to be followed-up as per protocol, Participant 1022 felt anticipation of symptoms was too bothersome, so he withdrew from the trial but was still followed up at the end of trial+6-month visit. Participant 1040 withdrew as adverse symptoms were too severe but agreed to be followed up at end of trial+6-month. Participant 1042 and 1054 withdrew from trial treatment due to severity of adverse symptoms but continued to be followed up as per trial protocol until the end of the trial. Participant 1005 withdrew because she concluded that her symptoms were not statin-mediated and restarted a statin, and participant 1036 withdrew because of intercurrent social stresses, due to worsening of gastric reflux not related to the trial and so discontinued treatment but was followed up at end of trial+6-months scheduled visit. The other 4 were withdrawn by the study team: 2 (participants 1037 and 1041) for declining to continue with the treatment months or failure to provide symptom scores despite repeated prompting, participant 1037 was non-compliant with trial procedures and was withdrawn from trial. Participant 1032 withdrew because of changes to other medications which rendered them ineligible, the participant's medical team planned to start him on more potent analgesia and so it was felt this made him ineligible because his new pain relief might mask adverse symptoms he had on the trial and participant 1035 withdrew because of post-operative complications from a series of surgeries after a road-traffic accident (prior to the trial) precluded him from following the protocol and as the participant was repeatedly non-compliant with the trial procedure he was withdrawn from the trial. The remaining 49 participants completed the trial and were included in the analysis. Participant 1041 was lost to follow-up. It was confirmed he was alive at his scheduled end of study+6-month visit date, hospital records showed he was still alive and had had recent attendances at clinic appointments within the hospital. Protocol deviations were reported for all participants who withdrew from the trial treatment.

5.4 Pill counts

At the end of trial participants returned their trial medication containers and pill counts were undertaken by the research nurse and verified by the study monitor. See Figure 25 for average monthly pill counts for participants who withdrew from the trial compared to those completing the trial. Pills remaining

at the end of each month were lower for participants completing the trial and increased number of pills remained among the participants who withdrew the trial treatment. The monthly median pill counts for completers and withdrawers are shown in Figure 26 and 27.

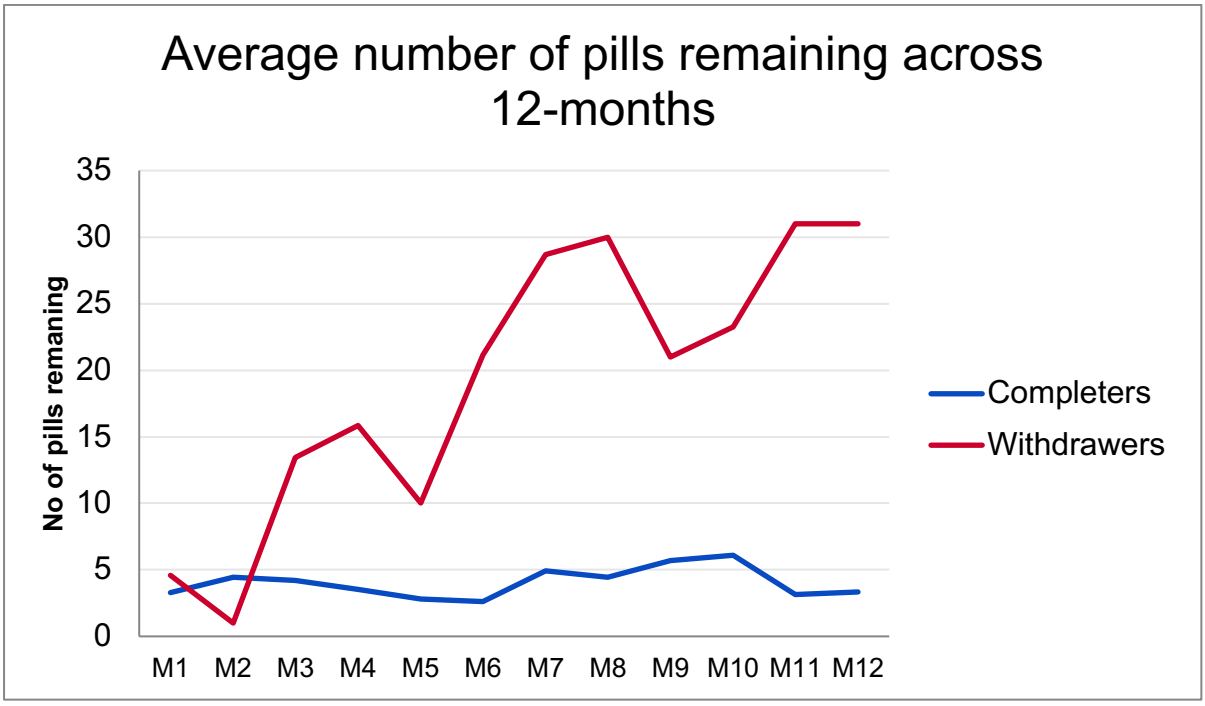


Figure 25: Average monthly pill counts for participants who withdrew the trial and those who completed the trial.

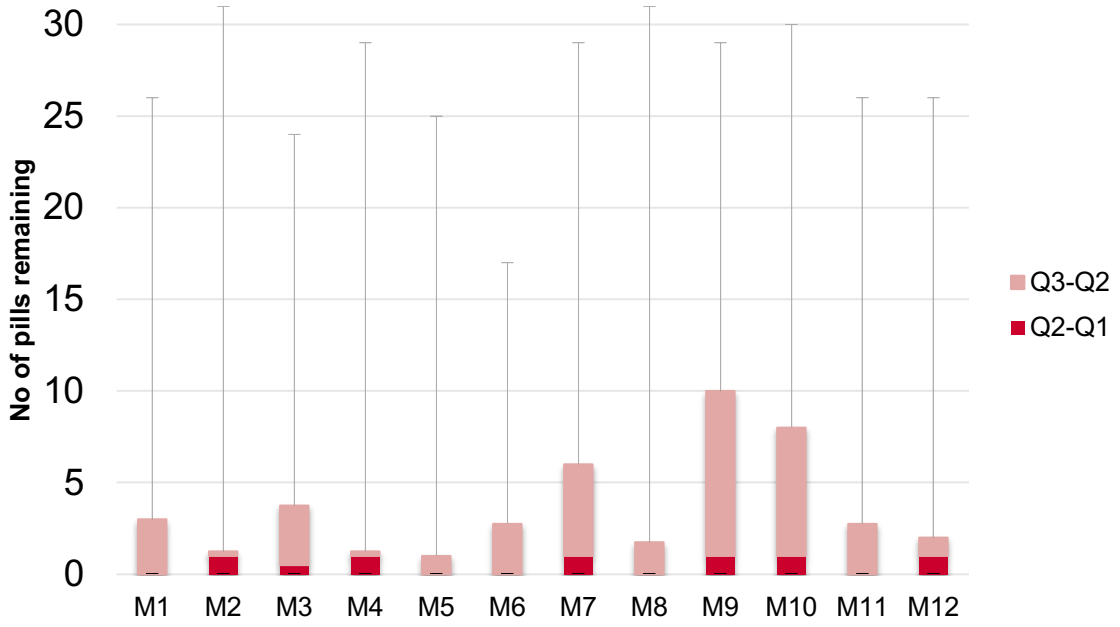


Figure 26: Median monthly pill count for completers with max/min and interquartile range

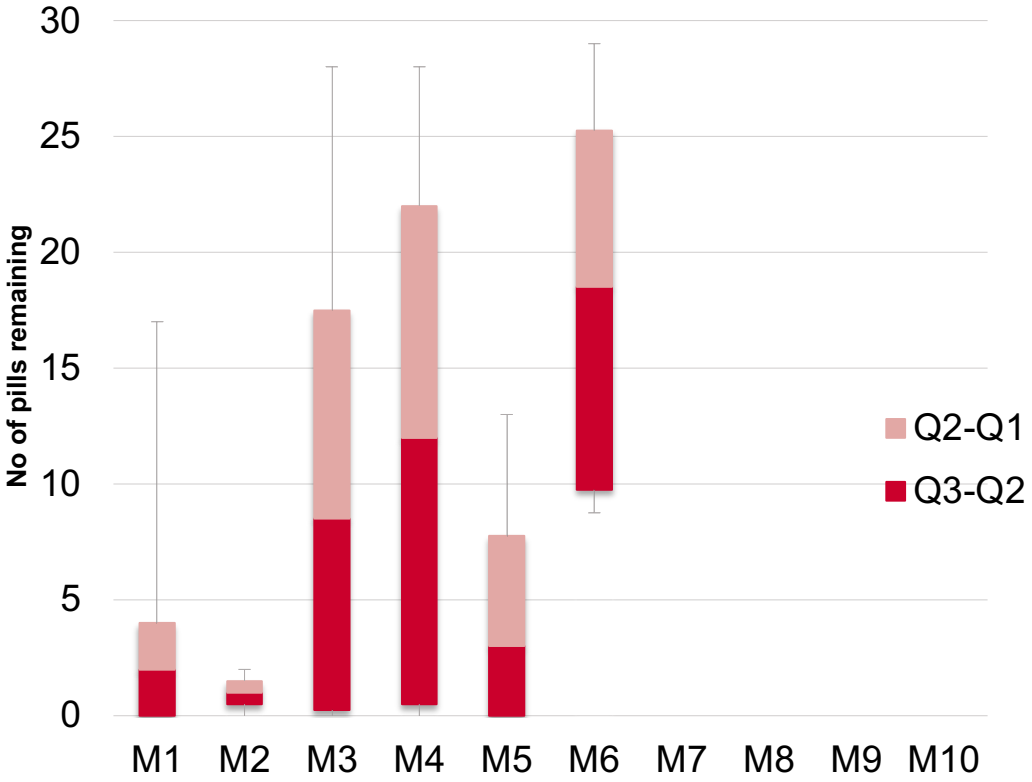


Figure 27: Median pill count by month for withdrawers with max/min and interquartile range.

5.5 Deviation from planned statistical analysis

There is no existing consensus on how to analyse n-of-1 trials (Gabler et al. 2011). In the trial, all patients showed higher symptom intensity on statin than no tablets, which violated the assumption behind the prespecified plan to calculate nocebo ratios individually, because the denominator became negative. The nocebo ratio was therefore calculated across all patients.

5.6 Nocebo Ratio

The nocebo ratio was 0.90 in the primary analysis. The comparison between statins, placebo and no tablet periods was performed under the four multi-level models, shown in Appendix 19. The fixed effect of treatment period (statin, placebo or no tablet) was statistically significant ($F=39.3$; $p<0.0005$) and explained 13.3% of the between-month variance. Allowing this effect to vary between subjects explained a further 7.8% of the between-month variance. In the final model, for 49 participants who completed the estimated marginal mean symptom scores for the three treatment periods were 6.3 for no-tablet months (95% confidence interval 2.8 to 9.8), 12.1 for placebo months (8.6 to 15.6; $p<0.0005$ versus no-tablet months) and 12.8 for statin months (9.3 to 16.3;

p<0.0005 versus no-tablet months; p=0.499 versus placebo months). However, see also Figure 28 showing results as intention-to-treat with all participants included (n=60).

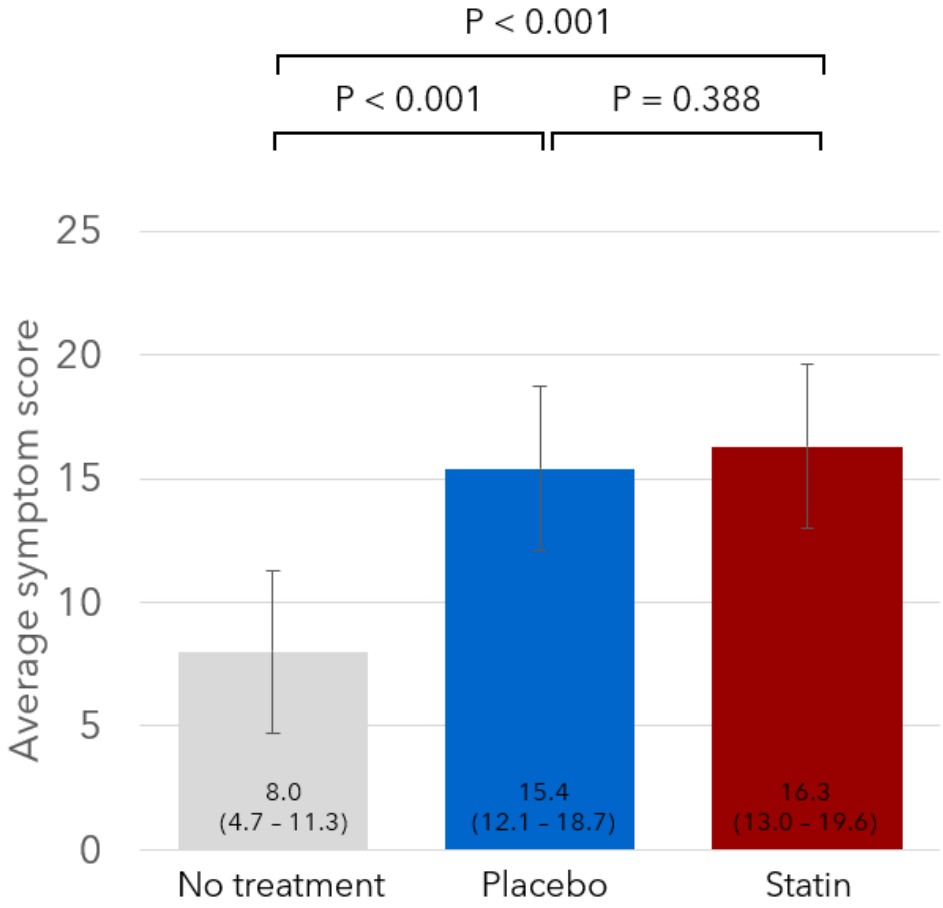


Figure 28: The mean symptom scores across the three treatment types. Whiskers indicate the associated 95% confidence intervals.

5.7 Missing data

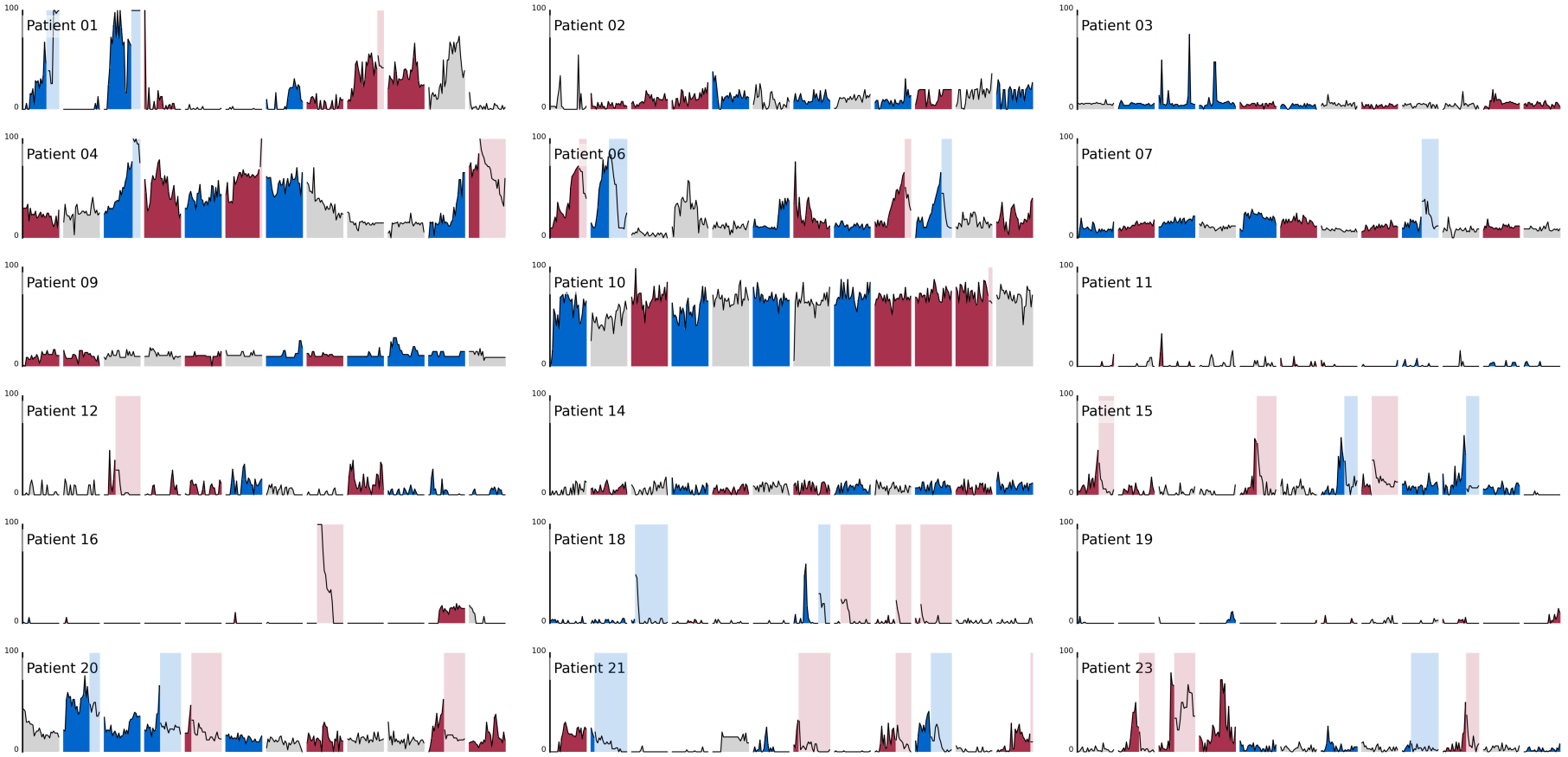
For a month of data to be included in the analysis, a participant had to have reported at least 10 scores on the phone application during the given month. Participants who had to stop their tablets early due to intolerable adverse symptoms but who continued to score were not excluded from the analysis, but their symptom scores following tablet cessation were not used. Within participants who satisfied these inclusion criteria, any further such attritional missing data were handled using multiple imputation by chained equations (Buuren and Groothuis-Oudshoorn 2011). Multivariate imputation by chained equation, creates multiple imputations instead of single imputations to take into account statistical uncertainty with the imputation. Missing values are replaced

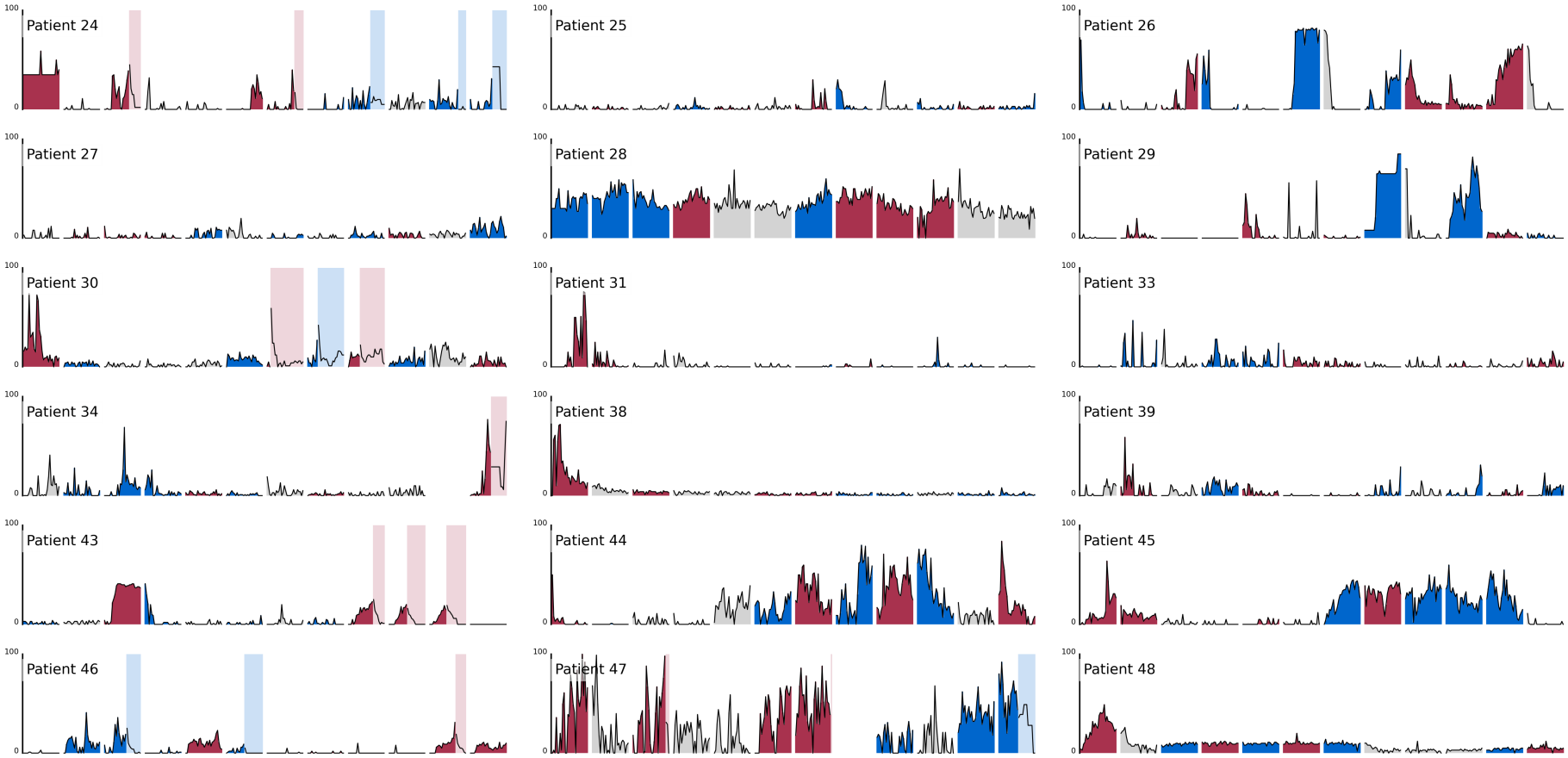
by predications from regressions that reflect relation in order to ensure the robustness and examine the sensitivity of the results to this choice, the analyses were rerun with the missing data imputed using last score carried-forward imputation, and again with missing observations simply excluded. In the trial, missing data felt likely to be associated with days where scores had changed. Commonly, participants stated that they always remembered to score if they had symptoms, therefore it was important to include attritional missing data to avoid overinflated scores that are a reflection of adverse symptoms making participant more likely to be prompted to score than on a symptom free day.

5.8 Daily symptom scores

Figure 29 displays the daily symptom scores for each of the 49 participants who completed the trial (the other 11 participants are shown in Appendix 18). Identification numbers were assigned at screening and are from 1001 to 1062 Participant 1008 and 1013 were screen failures and were not randomised to the trial.

Patients who completed the 12 month trial




Patient 24
Patient 25
Patient 26
Patient 27
Patient 28
Patient 29
Patient 30
Patient 31
Patient 33
Patient 34
Patient 38
Patient 39
Patient 43
Patient 44
Patient 45
Patient 46
Patient 47
Patient 48

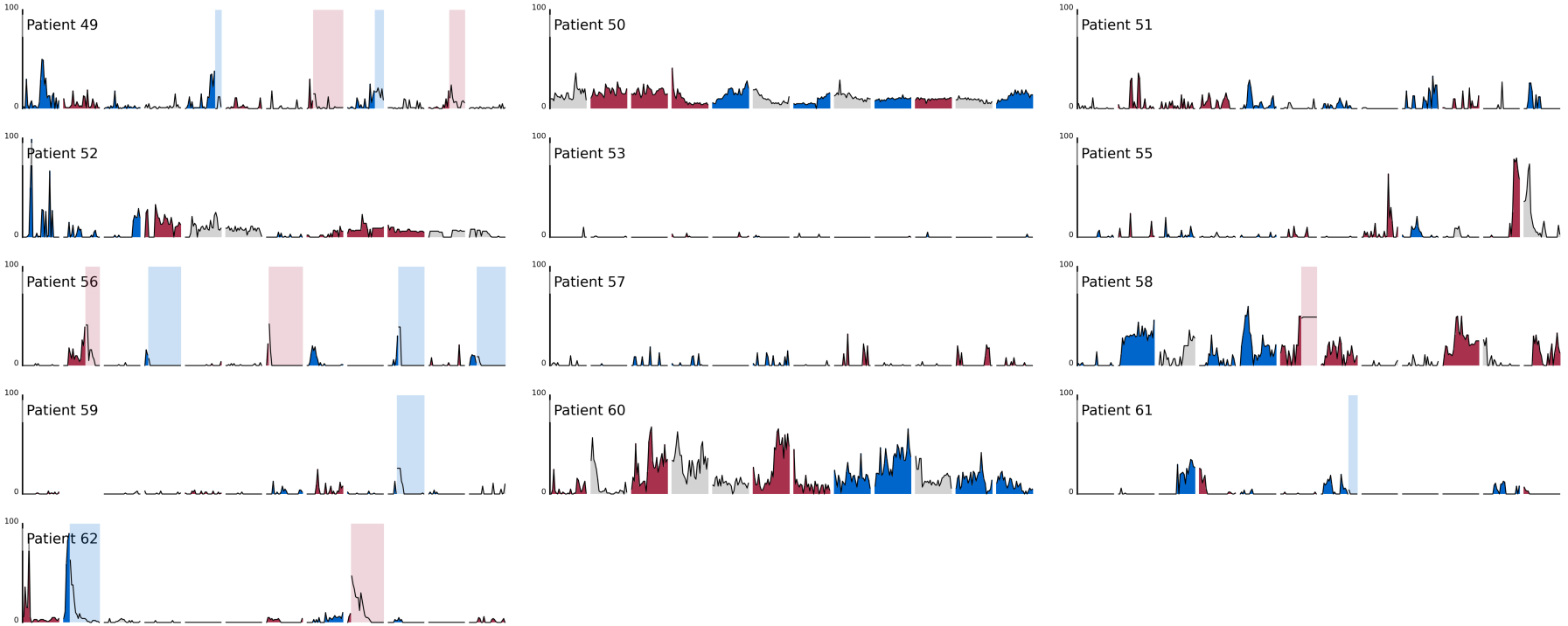


Figure 29: Every daily score in each of the 49 patients who completed the trial (labelled by their trial number)
The vertical axes represent symptom scores; the horizontal axes represent time (days separated into 12 monthly intervals). Symptom intensity bars are coloured grey in no-tablet months, blue in placebo months and red in statin months. Lighter shaded regions indicate that patients have stopped tablets early for that month due to intolerable symptoms. Each of the 588 bars represents a day (49 patients × 12 months) and shows the daily symptom scores of every single month (Howard et al. 2021, appendix p.7).

Figure 29 displays every daily score in each of the 49 patients who completed the trial.

In the trial 24 (49%) of the 49 participants who completed it stopped tablets early due to intolerable side effects for at least one month of the trial, with 71 stoppages in total. Across these 24 participants, the median number of stoppages was 3 (IQR 2 to 4).

Of the 71 stoppages, 31 were during placebo months (median days taken before stopping 18, IQR 9 to 21) and 40 were during statin months (median days taken before stopping 17, IQR 9 to 22).

Figure 30 shows the proportion of participants who stopped tablets over time whilst taking statin tablets (red) and placebo tablets (blue), following a period of no tablets (this sequence was not always present due to treatment order being randomised). Build-up and wash-out effects can be seen in Figure 31.

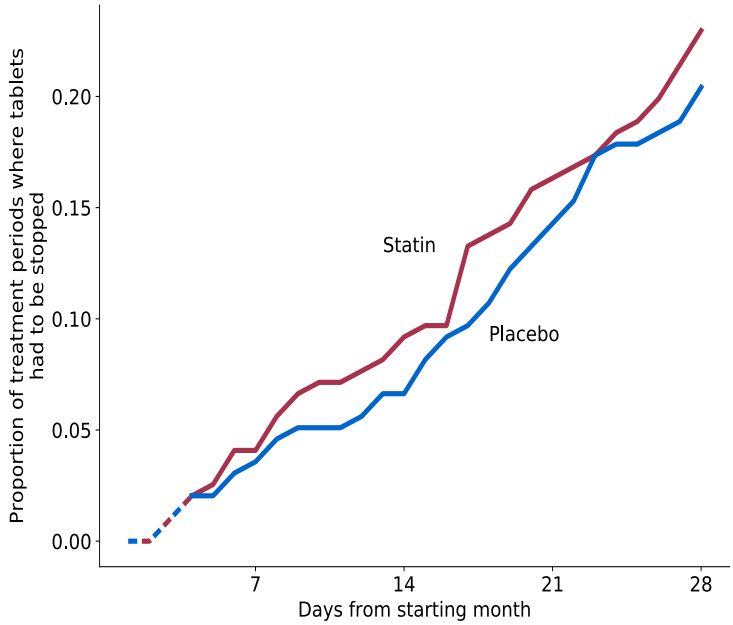


Figure 30: Graph showing proportion of treatment periods where tablets stopped following a period of no treatment

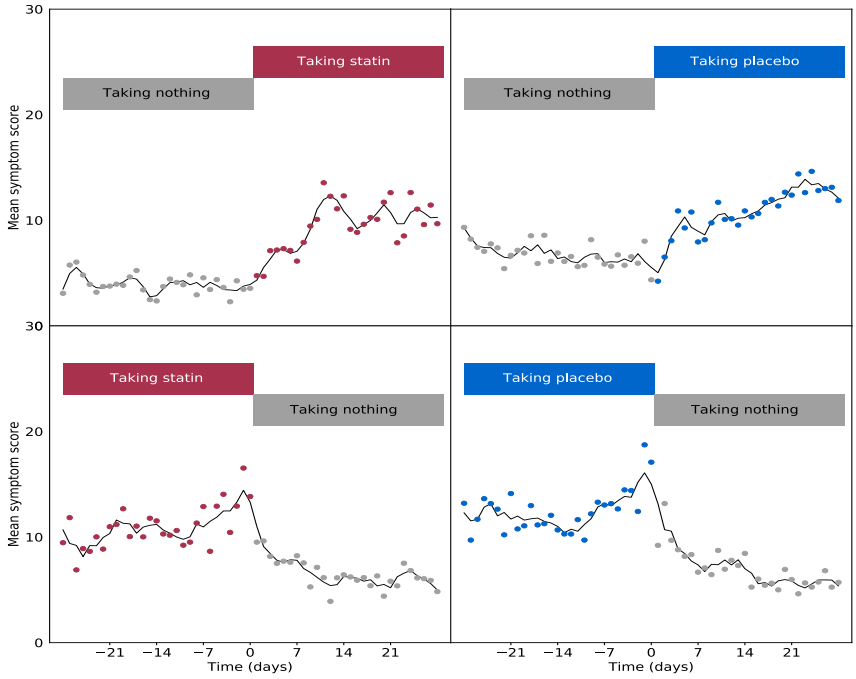


Figure 31: Time course of symptoms scores in days before and after tablets being started (upper panels) or stopped (either on schedule or early due to intolerable side effects; lower panels).

During tablet months, symptoms developed progressively over the days, regardless of whether the tablet was statin (Spearman's rho=0.98, p<0.001) or placebo (Spearman's rho=0.97, p<0.001).

Symptom relief on stopping tablets was prompt, with more than half (55%) occurring within three days, regardless of whether the tablet was statin (56%) or placebo (52%).

All serious adverse events, and adverse events judged severe, life-threatening or disabling, are shown in Table 10. No serious adverse events were deemed related to the trial procedures. The individual mean monthly scores by treatment period for each of the 49 participants who completed the trial are shown in Figure 32.

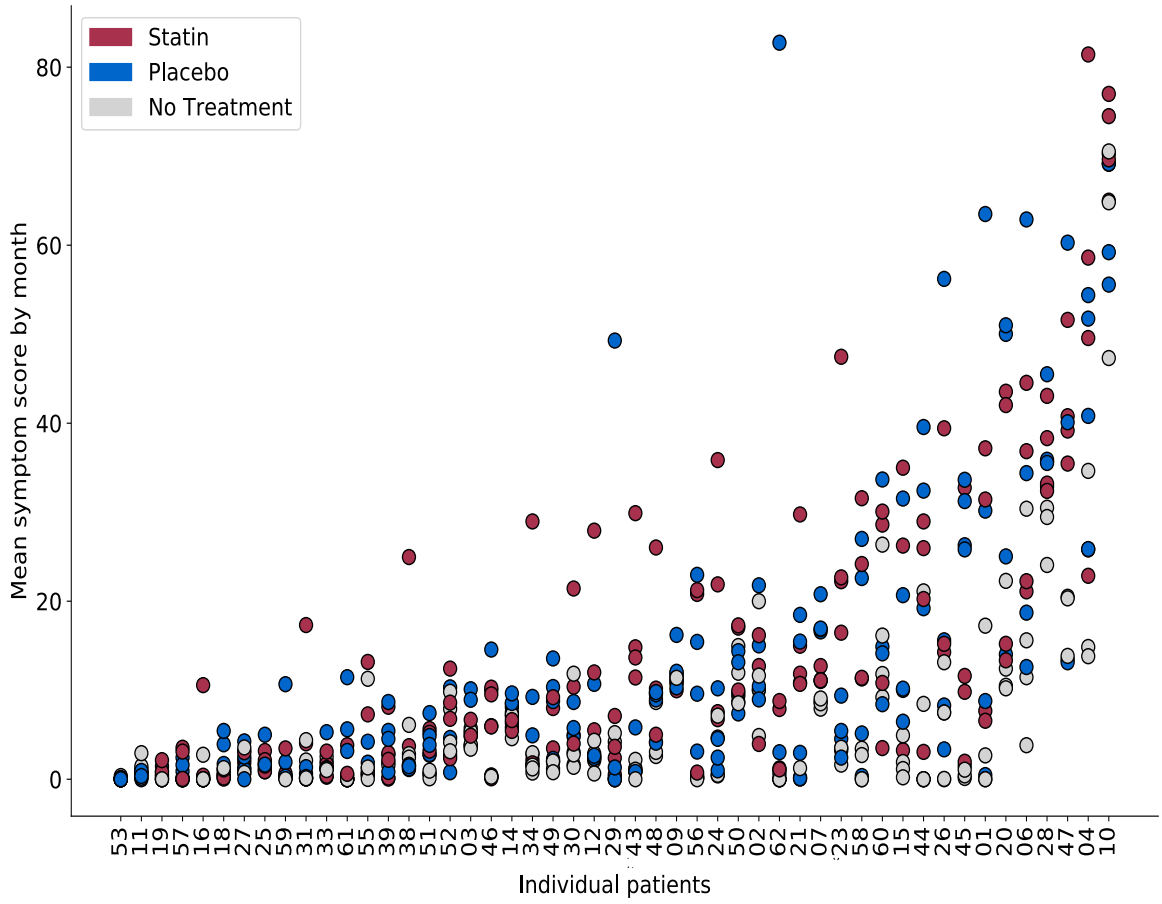


Figure 32: Each mean monthly score for each of the 49 participants coloured according to the treatment period (Wood et al. 2020 , p.2)

5.9 Inclusion/exclusion criteria

During the recruitment period of the trial, the eligibility criteria were not mistakenly violated. However, there were six patients who during screening were identified to meet the exclusion criteria. This was in relation to the exclusion criteria 'History of any condition that causes chronic pain'. Participants 1032, 1038, 1040, 1042, 1061, 1062 all fitted the criteria of having such a condition, which caused them chronic pain. However, the chronic pain symptom they experienced was entirely distinguishable from their previous adverse symptoms with statins. Therefore, during screening the chief investigator and study team deemed this exception to the exclusion criteria acceptable and went onto randomise them, reporting a protocol deviation for each participant. The study team clarified this with the Imperial Clinical Trials Unit operations manager and monitor before any randomisation took place.

5.10 Conduct of the trial

An automated update of the phone application in the May Bank Holiday of 2017 led to data loss for the first few days of that month. Protocol violations were reported for the few patient enrolled in the trial at that point due to lost data (1001-1007, 1009-1011) and automated updates on the server were permanently turned off.

5.11 Patient management or patient assessment

There were no participants who developed withdrawal criteria during the study but who were not withdrawn. There were no study drug dispensing errors. Each individual participant on the SAMSON trial, had a screening, randomisation, baseline, Month 1-12 visits, end of study and end of study+6-month visit. In terms of all but the screening and randomisation visit, the other 15 visits have a visit window that was scheduled to be short by the study team to ensure timely follow-up. The study nurse on the trial always ensured she telephoned for these visits within the visit window, but participants were often busy and put off the call. Therefore, with 1020 scheduled visits, it was inevitable a proportion would be late. If the nurse had any concerns, she would make an unscheduled contact prior to the monthly call. The nurse always made monthly contact within the visit window, but visits were sometimes later than the visit window if the participant was unavailable. Reasons included holidays and unwell relatives. The nurse reported late visits and numbers of days late for every participant.

The following deviations to protocol occurred during the trial:

- Participants 1035 and 1037 were both withdrawn for non-compliance with the trial protocol.
- Participant 1034 also repeatedly had significantly late calls, however this participant continued to score on the phone application and was a medical doctor and so was deemed able to assess serious symptoms that warranted urgent medical attention and so the chief investigator allowed her to continue to the end of trial.
- Participant 1034 reported on one tablet month she had been poorly adherent.
- Participant 1060 accidentally started the wrong month of treatment, rather than starting month 4, which was an empty container, she

accidentally began a tablet month. As study nurse, I identified this error, informed the patient and she stopped the incorrect tablet month, returned the partially used container and a new month 6 container was sent to her. The nurse clarified at the start of every new month each participant was on the correct container.

- Participant 1024 accidentally started the no treatment month 9 for the first two days of the month, rather than month 8 which was a 'tablet' month. I again identified this error, consulted with the doctor, and he advised as she still had 28 days left in the month, this was equivalent to a short calendar month and it was acceptable to start the correct tablets late.
- Participants 1024 and 1029 forgot to take their trial medication on a trip away. Participant 1044 thought he had forgotten to pack trial medication when he went on holiday but later discovered he did in fact have them in his suitcase. In all three cases where trial medication was forgotten, and as participants would have missed a substantial number of tablets, they were advised to remain off the tablets, when the mistake was discovered, for the rest of the calendar month and go on to the next month of tablets as planned.
- Participant 1005, 1027 and 1059 stopped trial medication for the rest of a given month due to hospitalisations not related to the trial or its procedure. They were advised to remain off the tablets for rest of the calendar month and go on to the next month of tablets as planned.
- Participant 1019 stopped trial medications on the 25th of one month, because his travel insurer would have invalidated his insurance if he had been on the trial medicines at the time of travel. The next month was a no treatment month so he completed his trip in the no tablet month and no further deviations were required.
- On day 1 of a new month preceding a 30-day month, Participants 1003 and 1005 accidentally continued and took the remaining tablet from the preceding month. Participants were retrained that medication containers include 31 tablets and on shorter months tablets may remain.

5.12 Adverse events

The objective of this trial was not to assess the efficacy of Atorvastatin 20mg daily. Furthermore, participants were selected for the trial only if they had had past adverse events with statins. Therefore, every month the study team confirmed all adverse events and serious adverse events, and these were reported even if deemed unrelated to the trial. See also Appendix 20 for adverse events by participant.

5.12.0 Brief Summary of Adverse Events

See Table 8 for a brief summary of adverse events by multilingual European Registration Agency (MEDRA) system organ class standardised terms.

Table 8: Reported adverse events for the SAMSON trial by MEDRA System Organ Class (SOC) standardised terms

System Organ Class	Frequency
Blood and lymphatic system disorders	2
Cardiac disorders	19
Ear and labyrinth disorders	1
Endocrine disorders	2
Eye disorders	11
Gastrointestinal disorders	67
General disorders and administration site conditions	58
Immune system disorders	5
Infections and infestations	47
Injury, poisoning and procedural complications	20* *Nil poisonings
Investigations	12
Metabolism and nutrition disorders	6
Musculoskeletal and connective tissue disorders	165
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1
Nervous system disorders	23
Psychiatric disorders	46
Renal and urinary disorders	9
Reproductive system and breast disorders	3
Respiratory signs and symptoms	3
Respiratory, thoracic and mediastinal disorders	44
Skin and subcutaneous tissue disorders	17
Surgical and medical procedures	19
Upper respiratory tract infections NEC	2
Urinary and renal disorders	1
Vascular disorders	16
Viral upper respiratory tract infections	1

System Organ Class	Frequency
Total	600

5.12.1 Display of Adverse Events
See Table 9 for frequency of MEDRA preferred terms for adverse events.

Table 9: Frequency of adverse events as coded by MEDRA preferred terms.
Frequency of adverse events as coded by MEDRA preferred terms.

Preferred Term (PT)	Frequency
Myalgia	76
Nasopharyngitis	41
Fatigue	29
Arthralgia	25
Muscle spasms	19
Sleep disorder	14
Cough	12
Diarrhoea	12
Headache	11
Fall	10
Pain in extremity	10
Abnormal dreams	8
Constipation	8
Urinary tract infection	8
Cognitive disorder	7
Dizziness	7
Nausea	7
Chest pain	6
Dyspepsia	6

Palpitations	6
Other symptoms	278
Total	600

5.13 Deaths, other serious adverse events and other significant adverse events

5.13.0 Listing of Deaths, Serious Adverse Events, and Other Significant Adverse Events

See Table 10 for listings of serious adverse events and Table 11 for other significant events (non-serious adverse events graded 'severe' or 'life threatening or disabling').

5.13.1 Deaths

At close-out of the trial, vital status of the 60 participants randomised to the trial was checked and no participants had died at time of trial close out.

5.13.2 Serious Adverse Events

See Table 10 for all serious adverse events that occurred during the trial or in the 6-months after the participant completed the end of study visit.

Table 10: Serious adverse events by the system organ and preferred term

System organ Class Preferred Term	Frequency during main study and 6-month follow-up
Blood and lymphatic system disorders	
Polycythaemia	1
Gastrointestinal Disorders	
Obstructive pancreatitis *	1
Infection and infestations	
Urinary tract infection	1
Influenza	2
Sepsis	1
Injury, poisoning and procedural complications	
Haemoperitoneum	1
Metabolism and nutrition disorders	
Iron deficiency	1
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Cholangiocarcinoma	1
Reproductive system and breast disorders	
Breast cancer	1
Surgical and Medical Procedures	

Tonsillectomy	1
Cardiopulmonary bypass	1
Shoulder arthroplasty	4
Transurethral prostatectomy	1
Vascular disorders	
Transient Ischaemic Attack	1
Myocardial Infarction	1

**Gallstone pancreatitis*

5.13.3 Other Significant Adverse Events

See Table 11 'Non-serious' adverse events that were graded 'severe' or 'life threatening or disabling'.

Table 11 Adverse events not categorised as serious but graded 'severe' or 'life threatening or disabling'

System organ Class Preferred Term	Frequency during main study and 6-month follow-up
Gastrointestinal disorders	
Abdominal pain	1
General disorders and administration site conditions	
Pain **	1
Nervous system disorders	
Multiple System Atrophy	1
Immune system disorders	
Anaphylactoid reaction ***	1
Reproductive system and breast disorders	
Ovarian cyst	1
Respiratory, thoracic and mediastinal	
Pleural effusion	1
Surgical and medical procedures	
Salpingo-oophorectomy bilateral	1
Hepatectomy	1
Cholecystectomy	1

**Biliary Pancreatitis*
***Worsening of pre-existing condition resulting in withdrawal from trial*
****Iron infusion*

5.13.4 Narratives of Serious Adverse Events

- Participant 1005 was hospitalised whilst abroad with biliary pancreatitis and hospitalised again 13 days later with a urinary tract infection. 1005 underwent a laparoscopic cholecystectomy and cholangiogram as a result of the biliary pancreatitis.
- Participant 1007 was hospitalised with a transient ischaemic attack. The participant had already completed the 12-months of the trial at the time of the event occurred.

- Participant 1027 was hospitalised twice for the same episode of confirmed influenza, after being discharged and readmitted. After the participant has completed the trial and was in the 6-month end of trial follow-up, the participant also had an elective bilateral tonsillectomy for histology due to an abnormal right tonsil on imaging. Biopsy results were reported to be benign.
- Participant 1033 was hospitalised during the trial with newly diagnosed polycythaemia.
- Participant 1038 had an elective right total shoulder replacement during the trial. After the participant had completed the trial, but within the 6-months follow-up period the participant was hospitalised and diagnosed with iron deficiency. Then had an elective hospitalisation for first stage revision of right shoulder hemiarthroplasty. 14 days later Participant 1038 was hospitalised again for sepsis and diagnosed with bilateral pulmonary effusion with atelectasis.
- After participant 1035 had already been withdrawn permanently from trial medication by the trial team, 1035 had a myocardial infarction whilst abroad, which required hospitalisation. On returning to the United Kingdom, he underwent an elective triple vessel heart bypass.
- Participant 1039 had two elective hospitalisations for right and then left total shoulder replacements.
- Participant 1044 had an elective hospitalisation for endoscopic transurethral resection of prostate (including cystoscopy).
- Participant 1059 was hospitalised with confirmed influenza whilst on the trial.
- Participant 1062 during the six-month post trial follow-up was admitted to hospital due to a cholangiocarcinoma for an elective right hemihepatectomy and cholestectomy.

5.13.5 Narratives of Other Significant adverse events

- 5-days before completing the trial, participant 1012 was diagnosed with Multiple System Atrophy. This was not considered a serious adverse event, as ‘results in persistent or significant disability or incapacity’ was not deemed to apply at the time of diagnosis, however the adverse event

was rated in terms of severity as ‘Life threatening and disabling’ as the condition was considered disabling.

- Participant 1010 had an anaphylactoid reaction to an iron infusion whilst on the trial. The participant was not hospitalised, but the event was considered ‘severe’.
- Participant 1032 had an exacerbation of pain, which was considered ‘severe’, and the participant’s medical team planned to treat with potent analgesia. The trial team considered in light of the planned new treatment the participant would likely no longer detect adverse symptoms caused by statins and deemed withdrawal from the trial the appropriate course of action.
- Participant 1038 hospitalised for serious adverse event and whilst in hospital she was diagnosed with bilateral pulmonary effusion with atelectasis. This did not prolong the participant’s admission but was considered to be ‘severe’.

5.13.6 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

None of the reported serious adverse events nor adverse events rated as ‘severe’, ‘life threatening’ or ‘disabling’ were considered ‘related’ to the trial IMP or the trial procedure.

5.13.7 Individual comparison on ‘severe’ symptoms experienced on statin vs. placebo months

See Table 12 comparing adverse events considered to be related to the trial tablets on month where placebo vs. statin tablets were stopped. It demonstrates that adverse symptoms were similar between placebo and statin months.

Table 12: Demonstrates the adverse events on months where placebo vs. statin tablet were stopped.

	Pre-trial		During 12-months of trial					6 mo after receiving own results		
			statin months stopped early		Placebo months stopped early		Did whole trial			
ID	1 ° or 2 °	Nature of adverse symptoms	N	Symptoms	N	Symptoms		Currently taking a statin?	Were original symptoms caused by statins?	Did trial help understand cause of symptoms
01	2 °	Back pain, dizziness, myalgia, bloatedness, memory problems, nausea, vomiting	1	Flatulence, bloatedness, Worsening bloatedness, indigestion	2	Indigestion, myalgia	Y	N - pain	Undecided	Still experiencing side effects
02	2 °	Chest pain	0		0		Y	Y	Y	Allowed to determine no side effects
03	1 °	Cramps	0		0		Y	Y	Y	In understanding past side effects

04	1 °	Myalgia, kidney cyst, loss of concentration, mood, sensory disturbance other than visual	2	Poor urine flow, insomnia, Memory loss, lack of concentration, Swallowing difficulty, loose bowel movements, lack of balance, fatigue, pain in lower body	1	Poor urine flow, insomnia, Memory loss, lack of concentration, Swallowing difficulty, loose bowel movements, lack of balance, fatigue, pain in lower body	Y	Y	Y	Provided focus on a dilemma of statins
05	1 °	Myalgia, malaise	0		0		Withdrew treatment- no results given (M6 onwards)	Y	Y	Withdrew trial and restarted a statin
06	1 °	Nasal congestion, skin tingling and dermatographism, myalgia	2	Rhinitis, headache	2	Rhinitis, myalgia	Y	Y	Y	Understand some of side effects in brain
07	1 °	Nausea	0		1	Exacerbation of nausea	Y	N- to start rosuvastatin as side effects with pcsk9-inhibitors	Y	Helped to see it might be nocebo
09	2 °	Myalgia	0		0		Y	Y	Y	All knowledge good

10	1 °	Myalgia	1	Myalgia	0		Y	No - trial results supported previous beliefs	Y	Helped clarify ever present vs. statin
11	1 °	Myalgia, nausea	0		0		Y	Y	Y	Proved statins not causing side effects
12	1 °	Myalgia	1	Tendonitis	0		Y	No- recent diagnosis of MSA	Y	Clarified Causation
14	1 °	Myalgia	0		0		Y	Y	Y	Unsure, cemented information already knew
15	1 °	Myalgia	3	myalgia	2	Prickly heat, myalgia	Y	Y	Y	Trial helped understand symptoms better
16	2 °	Myalgia, discomfort in calves	1	Myalgia	0		Y	No- Increased age means prepared to risk CVD	Undecided	Trial helped a little to clarify
17	1 °	Alopecia	0		0		Withdrew (M11 onwards)- received	Y	Y	Helped with causality

							partial results			
18	1 °	Weakness, tiredness	3	Myalgia, pruritus, fatigue	2	Tiredness, left side facial ache, myalgia	Y	N- restarted rosuvastatin and within 1-week symptoms	Undecided	Results helpful
19	1 °	Myalgia	0		0		Y	Y	Y	given confidence to take it long-term
20	2 °	Myalgia	2	Increased thirst, nasopharyngitis, sleep disturbance	2	Headache, Blurred vision, myalgia, constipation	Y	Y	Y	As some months ok and others not
21	1 °	Vivid dreams, disturbed sleep, myalgia, rash and hypersensitivity reaction (not including anaphylaxis or angioedema)	3	Dyspepsia, vivid dreams, sleep disturbance, pruritis, exacerbation of dyspepsia,	2	Dyspepsia, headache, vivid dreams, sleep disturbance	Y	Y	Undecided	Y: gave information. No: Symptoms

22	2 °	Decreased cognitive function, depression	2	Not recorded	0		Withdrew treatment (M6 onwards) - results not given	N - withdrew trial	Y	Good test of coincidence but could have been more blind i.e., no blank months. Test criteria did not adequately take account of patients suffering affective disorder you deliberately exclude it.
23	1 °	Vivid dreams, cramps	3	Pruritis, vivid dreams, myalgia, cramps,	1	Cramps	Y	Y	Y	Gave a definite answer that statins caused the symptoms
24	1 °	Myalgia, fatigue, crying	2	Fatigue, tearfulness, myalgia	3	myalgia, 'achy bones' fatigue,	Y-missed one month due to forgetting to bring trial IMP on holiday	N- never happy about them	No	Results inconclusive, symptoms low on some statin months and high on some placebo months

25	2 °	Eczema, sore weepy eY, eye dryness, bone pain,	0	0	Y	Y	Y	Useful got back on statin
26	1 °	Myalgia	0	0	Y	Y	Y	Helped identify statins not cause of symptoms
27	1 °	Arthralgia, diarrhoea, myalgia, aching arms and elbows,	0	0	Y (missed 1mo due to flu)	N - Total cholesterol 5.3mmo/l and high good cholesterol. GP advised statin not required at this time.	Y	If cholesterol ever high now would have no concerns about taking a statin.
28	1 °	Arthralgia, myalgia	0	0	Y	N-still not sure	Undecided	Outcome of trial not clear cut.
29	1 °	Headache, chest pain and tingling in left arm	0	0	Y-missed one month due to forgetting to bring trial IMP on holiday	N- started rosuvastatin but increased BP	Other	Confusing as swaps to BP meds during

30	1 °	Aches in back of legs,	2	Shin splints, ?myalgia	1	Myalgia	Y	N- results did not prove statin not cause	Y	3 of 4 statin months symptoms so reinforced beliefs
31	1 °	Myalgia in thighs	0		0		Y	Y	Unknown	Already knew statins cause but pleased could tolerate Atorvastatin
32	1 °	Muscle weakness, tremor, dry mouth, gynecomastia	0		0		Withdrew treatment (M3 onwards)- no results given	N-didn't complete the trial	Unknown	Only completed two months of trial -no treatment months
33	1 °	Mood disruption and memory loss	0		0		Y	Y	Y	Confirmed statins weren't cause
34	1 °	Aching legs	1	Myalgia	0		Y - missed one month as non-compliance with trial IMP for 1-month	N	Y	Side effects (on trial) caused by statins

35	2 °	Cramps and acid reflux	Unknown non-compliant with trial protocol	Unknown non-compliant with trial protocol	Unknown non-compliant with trial protocol	Unknown non-compliant with trial protocol	Withdrew treatment and non-compliant with study protocol (M7 onwards)-results not given	Y	N	Withdrew from trial so no results given
36	1 °	Malaise, depressed mood	1	Not recorded	2	Not recorded	Withdrew treatment (M11 onwards) - results not given	N	N	Withdrew and no results given
37	2 °	Fatigue	0		1	Myalgia, fatigue, irritable mood	Withdrew treatment and non-compliant with study protocol (M3 onwards)-results not given	N	N	Withdrew treatment and no results given
38	1 °	Arthralgia	0		0		Y	N-advised no longer required	Y	Y, helped determine

									statin not cause
39	2 °	Cramps in hand	0		0		Y	Y	Y	Successfully able to take statins now
40	1 °	Myalgia, rash and hypersensitivity reaction (not including anaphylaxis or angioedema)	2	Pruritis, myalgia, arthralgia, fatigue	0		Withdrew treatment (M5 onwards)- no results given	N- side effects with statins	N	Withdrew from trial
41	1 °	Muscle tightness	0		1	Urinary frequency	Lost to follow-up	Lost to follow-up	Lost to follow-up	Lost to follow-up
42	1 °	Myalgia	1	Myalgia	1	Depression	Withdrew treatment (M7 onwards) - partial results given	N-withdrew from the trial due to side effects	Y	Side effect even on 1/2 dose on trial
43	2 °	Dizziness, myalgia, nausea	3	Pain in limbs, light-headedness, myalgia, cramping	0		Y	Y	Y	Trial helped confirm statins were the cause

44	1 °	Myalgia	0		0		Y-missed one month due to forgetting to bring trial IMP on holiday	N-restarted statin and symptoms returned	Y	Trial helped determine caused effect
45	1 °	Myalgia, lethargy	0		0		Y	Y	Y	Showed statins not causing side effects
46	2 °	Myalgia	1	Fatigue, myalgia, flu-like symptoms,	2	Fatigue, low mood, myalgia	Y	Y	Y	Insight and new ways to manage statins
47	1 °	Gastrointestinal reflux, fatigue	2	Muscle weakness, trembling, malaise, raising heart, fatigue, myalgia, Exacerbation of general malaise, exacerbation of myalgia, exacerbation of arthralgia, exacerbation of	1	Alopecia, seborrheic dermatitis, heart rate increased	Y - missed one month of trial due to trial fatigue	N- (Trial showed) possible side effects	No	Unclear if did get statin side effects

				muscle weakness,						
48	1 °	Myalgia, fatigue, short term memory loss	0		0		Y	Y	Y	Trial results helped restart statin
49	1 °	Myalgia, tingling scalp	2	Lower back ache	2	Left bursitis of knee, lower back ache	Y	N - trial results and on alirocumab	Y	Most aching on statin months
50	1 °	Low mood, aggression, fatigue, low mood	0		0		Y	N-plans to restart, lockdown has delayed	Y	Proved statin might not be issue
51	1 °	Myalgia, cramps	0		0		Y	Y	Y	Symptoms again, ?build-up of statin
52	1 °	Back ache	0		0		Y	N -ongoing nausea, avoiding	Y	No symptoms on trial

							extra tablets		
53	1 °	Myalgia	0	0		Y	Y	Y	Helped clarify and restart a statin
54	2 °	Chest pain, myalgia, bleeding at back of nose	0	2	Breathlessness, leg pains, myalgia	Withdrew treatment (M9 onwards)- partial results given	N	Undecided	Restarted statin (after trial) but got new symptom
55	1 °	Knuckle pain, headache	0	0		Y	Y	Y	Helped see he should persist with statin
56	1 °	Muscle weak, decrease cognition, fatigue	2	Reduced cognitive function, fatigue	3	Reduced cognitive function, 'fuzzy head'	Y	N - restarted but joint pain, plans to restart a statin again in future	Y	Helpful to talk to doctors
57	1 °	Myalgia, nightmares, Upset bowels,	0	0		Y	N-, cholesterol ok if go up'll restart statin	Y	Not statin causing adverse symptoms

58	2 °	Myalgia, arthralgia, reduced cognitive capacity,	1	Exacerbation of sleep disturbance, muscle stiffness, dry eyes	0		Y	Y	Y	Trial results made restart a statin
59	1 °	Myalgia	1	Pain in hands and feet	1	Myalgia in hands and feet	Y- missed one month due to influenza	N- cholesterol not reduced on statins	Undecided	Felt results did not clarify
60	1 °	Aching limbs, nightmares, knee pain,	0		0		Y- accidentally started a tablet month in a no tablet month	Y	Y	indicated joint pain not statin related
61	1 °	Fatigue, nighttime cramps	0		2	Cramps, dizziness, tightness in calves	Y	N-GP not asked to restart	Y	Certain pains were not statin related
62	1 °	Myalgia	1	?Myalgia	1	Myalgia	Y	Y	Y	Has helped me into taking another statin

5.14 EOS+6-Month Follow-up

At their end of study +6-month visit 30 out of 60 participants (50%) had successfully restarted statins, 4 planned to do so, and 1 was uncontactable. The remaining 25 participants were off statins and not planning to restart, giving the following reasons: side effects in 18, cholesterol spontaneously improved in 4 (but no longer believed statins were causing side effects), a recollection that their cholesterol had not been reduced by a statin in 1, a new diagnosis of a progressive neurodegenerative disorder in another 1, and feeling themselves to be “too old” in 1 participant.

5.15 Chapter Summary

In summary, the results for the SAMSON trial have been reported and in Chapter 7 will be discussed and interpreted with recommendations made based on the results.

In Chapter 5, the results of the trial indicate that the majority of participants can tolerate and complete an n-of-1 trial. There was no significant difference in the mean score between the statin and placebo months but there was a significant difference between tablet and no tablet months. Fifty percent of participants were on statins after 6-months of completing the trial.

The analysis confirms that patients who discontinue statins due to side effects, do experience actual side effects but they are not caused by the pharmacological effects of a statin. Retesting using an n-of-1 trial, successfully enables half of the participants to restart a statin.

Chapter 6 will present the qualitative interviews with patients who declined or were not eligible for the trial and also a sub-study comparing the personality traits of those in the trial vs. those who declined trial participation.

6 The experiences of side effects in patients who continue and discontinue statins: a qualitative interview study.

6.0 Chapter overview

As literature is limited, this current study was undertaken with the aim to gain further understanding of the patients' experience of statin side effects. This is an area that cannot be explored entirely by clinical trials; patients may not be suitable or not wish to participate in interventional research. Thus, a qualitative study has potential to explore an uncharted area and generate hypotheses for future testing.

6.1 Method

6.1.0 Participants

Patients who were either ineligible or unwilling to participate in the SAMSON trial, were invited to participate in the interview study.

6.1.1 Recruitment Procedure

The London Brent Research Ethics Committee approved the study (REC 15/LO/1761). Recruitment to the SAMSON trial was from a wide variety of settings including GP practices, lipid clinics, cardiology clinics and Facebook advertising. The research nurse invited patients who were not recruited to the SAMSON trial to face-to-face or telephone interviews. The aim was to recruit approximately 20 participants and continue to recruit until data saturation was reached and no new themes were arising.

6.1.2 The interview

Participants were given a participant information sheet (information sheets and consent forms can be seen in Appendix 21). When given an information sheet, participant were given at least 24-hours to decide whether they wished to participate. Prior to the interview starting, the research nurse (myself) received written informed consent from the participants. I have previous experience of conducting and analysing qualitative interviews. After informed consent, I followed a scripted information text, designed to sound natural but with the aim to maintain consistency when explaining the purpose of the interview. Basic demographic information was collected, and I followed a semi-structured topic guide (see Appendix 22), designed to ask open-ended questions with pre-

determined probing questions to explore responses in more detail whilst attempting to avoid leading questions. The topic guide was designed by the research nurse and reviewed by specialists in qualitative analysis and cardiovascular disease prevention before use.

6.1.3 Data Analysis

Audios recordings of the interviews were made and then they were transcribed verbatim. The interviewer then checked the accuracy of the transcriptions by listening to the audio-recording whilst reading the transcripts. The transcripts were then analysed using Thematic Analysis (Braun and Clarke 2006). The researchers assumed a critical realist approach (Lawson et al. 1998). The study nurse inductively coded line-by-line the first 9 interview transcripts, coding each unit of meaning using Nvivo software to organise the codes. The study nurse assigned the text into themes and sub-themes for each transcript and refined and restructured themes and sub-themes on an ongoing basis as each new transcript provided more context to the analysis. Two degree-graduated student nurses (ZK, LB) also analysed a proportion of the 9 transcripts each and met to discuss and agree themes and sub-themes. A fourth researcher (CN), an expert in qualitative analysis, oversaw this meeting. Themes arising were deemed broadly similar across each researcher's analyses and therefore valid and so an overarching framework for the analysis was created. The study nurse then completed the rest of the interviews and coded all further interviews within the established framework, with only minor adjustments made. The study nurse avoided reviewing the existing literature until the coding framework was finished to prevent bias.

6.2 Results

19 participants were recruited. Eight completed the interviews face-to-face and 11 completed it by telephone. The mean interview length was 30 minutes (range 5-68 minutes). Demographic information about the participants is shown in Table 13.

Table 13: Demographic information for participants in the interview study.

Mean age	65 Years old (SD 11)	
Gender	Male	12
	Female	7

Ethnic origin	White-British	14
	White-other	4
	Prefer not to disclose	1
Highest completed level of education	Secondary school	7
	Undergraduate degree	6
	Technical/vocational	4
	Postgraduate degree or diploma	2
Statin history		9
	Stopped statins due to side effects	
	Currently on statins	4
	Never had side effects	
	Previous or current side effects	6

The analysis is presented in terms on the themes and subthemes (or domain summaries) in Figure 33. Data are presented by themes and subthemes below with verbatim quotes in Tables 14 and 15 to support the analysis.

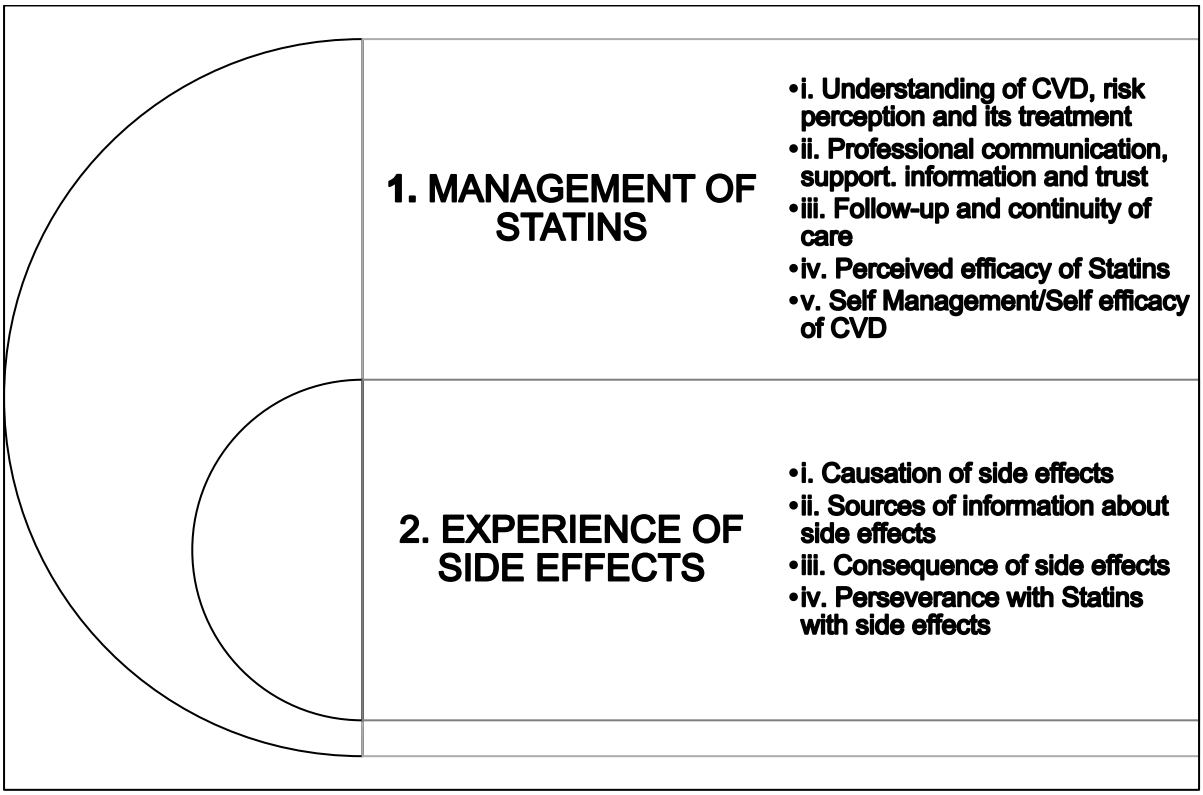


Figure 33: Diagram showing hierarchy of themes and subthemes of the analysis

6.3 Management of statins

'Management of statins' was a prominent overarching theme covering a plethora of sub-themes related to the organisation and coordination of the prescription and management of taking statins including patients' self-management, understanding of cardiovascular disease and patients' experience of health care and interaction with health professionals and others.

6.3.0 Understanding of cardiovascular disease (CVD), risk perception and its treatment

Participants stated various reasons for taking statins, including reducing their risk of a cardiovascular event (quote 1), mortality (quote 2) and cholesterol (quote 3). Some participants were unclear if statins were something they would need to take on a longer-term basis (quote 4). One participant suggested their cholesterol level was pivotal to whether they restarted a statin (quote 5) without the participant considering any wider cardiovascular risk as an indication to take statins.

6.3.1 Professional communication, support, information and trust

When participants had side effects, communication with health care professionals was considered important by participants because they valued the opinion of their doctors. However, some participants said they really had to persuade a doctor that the statin might be the cause of their side effect (quote 6).

If a participant's doctor dismissed a perceived side effect as unlikely to be related to the statin, it could lead participants to feel at an impasse and lead them to take unsolicited action without informing their physician (quote 7). One participant raised concerns about their GPs' motives for prescribing statins (quote 8). Participants discussed the back and forth of going to see the doctor about their side effect, with the patient explaining their concerns about statins and the doctor explaining their concerns about them not taking statins (quote 9). Many participants discussed conflicting information from other sources as undermining the advice given by doctors and some participants suggested an N-of-1 trial could be a potential way to resolve this uncertainty (quote 10).

6.3.2 Follow-up and continuity of care

Follow-up care was discussed as an important and positive aspect of prescribing statins. Participants preferred to have continuity in their care and to

see the same prescriber about the same issue and to be known to their health care provider (quote 11). Participants also liked continuity in statin prescriptions and disliked getting alternative brands of statin because packaging was different and could lead to errors with adherence (quote 12). Follow-up care surrounding statins was deemed to be poor by some participants who said they were put on statins and left without follow-up or assessment of whether the statin was actually effective (quote 13).

6.3.3 Perceived efficacy of statins

Participants judged efficacy of statins by their reduction in cholesterol or absence of myocardial infarction, stroke or death. Some participants also judged efficacy by not having any side effects. It was common for participants to estimate how much of a reduction in their cholesterol level was associated with the statin and how much was due to other lifestyle factors (quote 14).

statins were seen positively if cholesterol levels were reduced while on them especially if a low cholesterol diet had previously failed to lower cholesterol, but participants saw statins less positively if cardiovascular disease progressed despite taking them. One participant had concerns about the risks of cholesterol being too low (quote 15).

6.3.4 Self-Management/Self Efficacy of CVD

Participants described self-management of their condition with attempts to modify diet, control weight, exercise and also research about their medical conditions and treatments (quote 16). One participant undertook self-management of cholesterol in his diet when he deemed statins to be ineffective because his cardiovascular disease progressed despite taking statins for years (quote 17). Some participants were unable to control their cholesterol with diet alone (quote 18).

Table 14: Management of statins' sub-themes with verbatim quotes from participants

Understanding CVD, risk perception and its treatment	Quote 1	**…They're great for reducing the heart attack risk and risk of strokes** 006, female, 36 years old, taking statin despite side effects
	Quote 2	**Well, I think it's helped my cholesterol… I'm 68 [68th year] I'm still here. I've beaten all my family, I'm the oldest female in my family now. So, something must be going right** 013, female, 67 years old, taking statin despite side effects
	Quote 3	**Interviewer: …What was the reason that you'd started to take statin?** **Respondent: I think my cholesterol was fairly high. I can't remember whether it was eight point something. I can't remember. Last time it was 6.7.** 008, female, 73 years old, stopped statins due to side effects
	Quote 4	**Well, I'm going to ask my GP next time, "Do I still need to take them," because I don't know if it's an on-going situation, that it's a permanent thing** 015, female, 76 years old, taking statins never had side effects with statins
	Quote 5	**I had one in September, which gave a reading of 5.4, which my GP was reasonably happy with. I'm going to go to a pharmacy and have my own cholesterol test done, now I've not been on statins for a few weeks, and just see what the level is then. If it's gone up a lot, I would go back on statins and put up with the aches and pain.** 016, male, 73 years old, stopped statins due to side effects
Professional communication, support,	Quote 6	**…the muscle pains … I couldn't even tuck my shirt in, …But it did take me a bit of time to convince the GP though to start with…The statins were giving me the problems…I virtually**

information and trust		**had to underline it and take the leaflet and underline the bits where I thought was giving me the problem on the side effects. But then we did try another one, and so on, and that gave me the same problems, so I think in the end they realised it was either me mentally, or it was the statins.** 017, male, 67 years old, stopped statins due to side effects
	Quote 7	**I found that my memory was just absolutely tanking, …I saw [doctor]… and he said, "That's not possible." I think he said, "Obviously, a statin doesn't actually enter your brain, so it's not possible." … But I was really convinced that it was because of the statin, so again, I just took myself off it. I didn't mention it to him, because obviously, I only see him every six months or once a year** 006, female, 36 years old, taking statin despite side effects
	Quote 8	**I sometimes wonder whether they [doctors] get a little bit of money for pushing statins?** 017, male, 67 years old, stopped statins due to side effects
	Quote 9	**Yes, at the minute I'm on Atorvastatin and I'm having a ping-pong with Doctor xx… … because of these side-effect…I do consider what [doctor] says. "Well, it could save your life." … This is what we don't know, isn't it?** 012, female, 83 years old, still taking statins despite side effects
	Quote 10	**I think the research you are doing [SAMSON trial] is very good because it might sort of, put people's minds at rest. You know people who can't take statins. If it's sort of found there isn't**

		any problem at all … I mean as I was told by a doctor, you sort of think, that's one doctor saying one thing and then another doctor saying another. 019, female, 72 years old, stopped statins due to side effects
Follow-up and continuity of care	Quote 11	**I just think it's nice to see the same doctor about the same thing** 001, female, 73 years old, stopped statins due to side effects
	Quote 12	**I have a prescription; I seem to get a different make. Not every time, you know what I mean. Regularly, it's a different brand comes through. Not all of them are marked 'Monday, Tuesday, Wednesday, Thursday, Friday'. So, the only difficulty that some of the prescriptions give is that occasionally I can't remember whether I did or didn't take the statin tablet.** 004, male, 60 years old, never had side effects with statins
	Quote 13	**…they seem to put you on it, and just leave you on it, don't they?** 001, female, 73 years old, stopped statins due to side effects
Perceived efficacy of statins	Quote 14	**I've seen a reduction in cholesterol, which I think is directly linked to taking the statins. Because my diet didn't change significantly through that period.** 004, male, 60 years old, never had side effects with statins
	Quote 15	**… It was down to about 1%, and 1.3% or something, total cholesterol. I used to say, "Isn't that too low? The body makes cholesterol because it has a reason." I was told, "No, the lower the better. You're doing fine.**

		018, male, 72 years old, stopped statins due to side effects
Self-management/self-efficacy of CVD	Quote 16	**I read an article that said that statins could have this side effect so when I changed to the morning, taking the tablet in the morning, it felt better overall.** 011, male, 49 years old, still taking statins despite side effects
	Quote 17	**…The atherosclerosis was still progressing, and I wanted to stop the progression [by plant-based diet] so I looked at what I could do to stop further progression. That's what I'm trying to do…** 009, male, 68 years old, stopped statins due to side effects
	Quote 18	**I was trying to control it by diet and exercise. But even though diet and exercise had a good impact in the first couple of months, then it just resettled quite high. They've said that it's possible familial hypercholesterolemia.** 006, female, 36 years old, still taking statins despite side effects

6.4 Experience of side effects

'Experience of side effects' is a sub-theme of the main theme 'Management of statins'. It covers all second-tier sub-themes related to patients' experience of side effects regarding statins. See Table 16 for verbatim quotes from participants for each subtheme.

6.4.0 Causation of side effects

Starting a statin at the same time that an adverse symptom occurred led to some participants considering the statin might have caused it (quote 19). Participants also considered statins as a potential cause if when the statin was stopped the side effect also subsided (quote 20). Participants who took no other medications except statins or who had ruled out their other medicines as the cause, were more convinced that their statin caused their side effects (quote 21). Some participants discussed uncertainty about the cause of adverse symptoms because of other factors such as ageing, an underlying medical condition or a symptom persisting after the statin was stopped.

6.4.1 Sources of information about side effects

Participants spoke of their friends' and families' experience of side effects with statins as being influential for them (quotes 22 & 23). The Internet and information leaflets were also sources of information about statins (quotes 24 & 25). Reports in the media were mentioned as influential and sometimes conflicting with the medical advice they were given (quotes 26 & 27). Some participants had self-referred to the SAMSON trial after reading a British Heart Foundation article about it; the article also discussed the nocebo effect, and this led to the participants who had read the article considering the nocebo effect as a possible alternative cause of their adverse symptoms (quotes 28 & 29) and this was a new concept to some of the participants.

6.4.2 Consequences of side effects

Some participants had experienced distressing side effects with statins (quote 30). A few participants stated that even if the source of the side effect was psychological rather than pharmacological it was still very disruptive to their activities of daily living (quote 31). One participant who had raised liver enzymes and jaundice while taking statins was advised she should never take statins again (quote 32). The consequences of this jaundice were quite wide-

ranging and led to the participant becoming unemployed and clinically depressed (quote 33). Stress was seen to exacerbate adverse symptoms (quote 34).

6.4.3 Perseverance with statins despite side effects

Some participants who had adverse symptoms persevered with statins despite side effects. Side effects were managed in various ways such as changing the time of day they took statins, changing to a different type of statin or treating the adverse symptom. Some participants tolerated adverse symptoms because their cardiovascular risk was high (quote 35).

Table 15: Experience of side effects sub-themes with verbatim quotes from participants

Causation of side effects	Quote 19	**erectile dysfunction…I can't be certain that's because of that, but it happened about the same time I started taking them** 010, male, 63 years old, still taking statins despite side effects
	Quote 20	**I just said to the doctor, "Look, I just don't think I, I'll take them any more…And he said, "Fine, we'll give it a couple of months." And I, within a few days- … I was back to normal… It was really that different, yeah** 001, female, 73 years old, stopped statins due to side effects
	Quote 21	**I started on blood pressure tablets at the same time, but they've changed them over the years to different ones, so I've ruled them out. The only one I've been on permanently is the statin, so that's why I think the side effects are related** 010, male, 63 years old, still taking a statin despite side effects
Sources of information about side effects	Quote 22	**I didn't connect it…and what really made me say about it was my cousin, who'd had had a similar experience, her doctor took her off it straight away, to see if it was that.** 001, female, 73 years old, stopped statins due to side effects
	Quote 23	**Like they say, you shouldn't take anybody else's medicine and stuff like that, and I suppose you shouldn't take anybody else's opinion. But it just happens I've got a friend and he's had more open-heart surgery and stuff like that than anybody, I would say. He always says to me, "Don't take statins,"… But I suppose you should perhaps not listen to it, but you take it on board'.**

	012, female, 83 years old, still taking statins despite side effects
Quote 24	**Yes. I get severe itching all over my body, which it doesn't say is a side effect, but I think it is. I've actually Googled it and there are loads of people saying the same.** 010, male, 63 years old, still taking statins despite side effects
Quote 25	**Obviously, I read the leaflet. I mean, I always say, if you read all the leaflets with the possible side effects of any drug, you wouldn't take them. You know, it's quite frightening when you read the leaflet that comes with these drugs, as to the possible side effects. I go through the list. I, sort of, cross them off, "No, I don't get that, I don't get that." Disturbed sleep, strange dreams, appears to be one side effect of statins, but I think most of us get those anyway, whether we take them or not, so that doesn't worry me particularly, no.** 016, male, 73 years old, stopped statins due to side effects
Quote 26	**I'm wanting to know is there a definite opinion on them? Because you read the papers and they say everybody should be on them. Next day you read it, everybody shouldn't be on them. Depending on which celebrity doctor you believe.** 012, female, 83 years old, still taking statins despite side effects
Quote 27	**… Sometimes some say that we should have them, and others say nobody should have them, so I don't know. You never quite know when you read these things in the press and that which way, who's sponsored the things, or the article and what have you.** 017, male, 67 years old, stopped statins due to side effects

	Quote 28	**Like I think it said in the article, if you're on a placebo, and you end up feeling the same as you did when you were on statins, then it's obviously not the statins causing your aches and pains. That interested me** 016, male, 73 years old, stopped statins due to side effects
	Quote 29	**Well, after reading a bit in the British Heart Foundation thing, I wondered whether it was just purely down to my mind in the end, because the first part of it certainly wasn't, but I wondered whether it was the thought that if I take this I will get the pains, I don't know.** 017, male, 67 years old, stopped statins due to side effects
Consequences of side effects	Quote 30	**I'm very keen to take statins. I've got nothing against statins. I'm not a statin warrior, or anything like that. I'd love to take statins because I believe the statistics, but the side effects got such that sometimes I couldn't really tell where my foot was in relation to my ankle and, you know, I started stumbling on stairs, and things like that.** 018, male, 72 years old, stopped statins due to side effects
	Quote 31	**Even if you gauge it incorrectly, even if it's the Nocebo thing or whatever it is, my memory was absolutely shot…** 006, female, 36 years old, still taking statins despite side effects
	Quote 32	**I was yellow, my head, my eyes, everywhere, fingernails, the lot** 007, female, 69 years old, stopped statins due to side effects

	Quote 33	**… my employment had ceased, because, obviously, they only pay you up to so much. So, by that time, you know, they'd stopped paying. … I saw this Dr … before, and I had to continue seeing him. I suppose you feel fed up that you have to go back on pills for your nerves ...** 007, female, 69 years old, stopped statins due to side effects
	Quote 34	**I was quite down at the time anyway, because my husband only died several years ago…So you're thinking, like, four years ago, when I started going on statins…And so, erm, it was stress of everything else, you know what I mean?...So I thought a lot of it was 'cause of that… but it, it was definitely the statin.** 001, female, 73 years old, stopped statins due to side effects
Perseverance with statins with side effects	Quote 35	**Interviewer: can you tell me the reason you've continued to take statins?** **Participant: Because I'm scared not to. I'm worried of the implications of stopping. I've never asked my GP if I should carry on. I do blood tests, obviously, three times a year with my diabetes and that is always monitored…I keep taking them, because everything is okay… I've got family-health issues with heart attack, strokes and things like that, and diabetes. So, yes, I carry on. I take them every single day.** 013, female, 67 years old, still taking statins despite side effects

6.5 Personality sub-study

The generalisability of the SAMSON trial results and also the utility of the intervention to the general population are important considerations. This is particularly significant as there was a high refusal rate among patients invited to the trial. It is important to consider if patient characteristics, co-morbidities and outcomes of the trial reflect the general population. For example, one issue of generalizability of the findings of the review in Chapter Two was that in psychology trials there is often the use of young and healthy volunteers without comorbidities. Therefore, such results are not translatable into clinical practice. This leads to difficulty of cross-disciplinary working. In medicine, individual or pooled RCTs are considered to be the highest level of evidence for assessing treatment efficacy and can influence policy recommendations. However, a review of studies which had attempted to compare RCT participants to samples in clinical practice, found that 71.2% of studies explicitly stated in their results that the RCT was not broadly representative of the real-world (Kennedy-Martin et al. 2015). This has potential implications for the findings of trials, with patients with comorbidities who might be prone to side effects being excluded from trials. In some contexts, younger participants, with less comorbidities and reduced risk of mortality are selected for trials whereas patients resembling the 'real-world' population might be excluded. There are explicit traits or eligibility criteria for selection of participants to any clinical trial. For the SAMSON trial, every attempt was made to keep the eligibility as wide as possible, for example, there was no upper age limit and different types of side effects were acceptable. Furthermore, travel was reimbursed to encourage patients from all socio-economic statuses and young and working patients were encouraged to participate by making the number of physical visits to the site limited. However, factors that must be considered as major factors for refusal are concern about side effects and also concern about using a mobile phone device, that could put off elderly patients or the less technically able. Interestingly, RCT patients in a phase 1 trial were found to have personality traits that were more receptive to novel experiences (Kushner et al. 2009). There is scarce literature on the difference between trial participants and the general population. Evidence from a systematic review shows that the personality trait of optimism can correlate with the placebo effect and anxiety with the nocebo effect (Kern et al. 2020). However, anecdotal evidence suggests there

might be high levels of conscientiousness among trial participants. The SAMSON trial showed that 90% of side effects are nocebo related and means that it is important to understand if this trial is attracting certain personality types to participate and putting off others, this sub study aimed to investigate if there are differences in trends in personality factors between trial participants and those declining the trial in order to understand the generalisability of the results.

6.5.0 Hypothesis

There is no difference in personality factors between participants in the trial and those who have refused to take part in the trial (who fit the eligibility criteria).

6.5.1 Study objectives

Determine if there is any difference in personality trait in those in the trial and those who refuse the trial.

6.5.2 Method

Consecutive participants were invited until 20 participants were recruited for each group. Group 1 was SAMSON trial participants and Group 2 people who declined the SAMSON Trial because of concerns about restarting a statin. Any participant who explicitly said they did not wish to be re-contacted was not invited to the sub-study.

Participants were sent a brief information sheet and if agreeable signed consent and completed a brief demographic form and the Mini-IPIP (Donnellan et al. 2006). The Mini-International Personality Item Pool (IPIP) is a 20-item short form of the well-established and well-validated 50-item scale measuring the big five factors of personality (Extraversion, Agreeableness, Conscientiousness, Neuroticism, Intellect/Imagination). It was chosen because it was a quick and easy to complete scale but is a shortened version of a very well-established scale. Responders were asked to return the questionnaire via a freepost envelope. All responders received a £20 gift voucher after completion. This study was submitted as a substantial amendment to the main trial and was approved by the London-Brent NHS research ethics committee.

6.5.3 Analysis

Based on Mini-IPIP recommendations, the total sample mean and SD was to be calculated for each of the five factors and participants, would be within 1-half SD of the average will be labelled ‘average’ and those above or below labelled ‘high’ or ‘low’ respectively. Difference in ‘low’, ‘high’ and ‘average’ scores for extraversion,

agreeableness, conscientiousness, neuroticism and imagination/intellect would be compared between the two groups. This was planned to be a preliminary investigation to determine if there is any indication of differences between groups and as such no power calculations were undertaken.

6.5.4 Results

29 patients who declined to take part in the trial (but the researchers had contact details) because of concerns about restarting a statin but who had been identified as eligible were invited to the sub-study. Only 5 replied to take part. It is unknown the reason for the others declining. Consecutive trial participants were invited once they had completed the trial, due to the low number who responded in the 'declined' group not all vouchers were used, so recruitment continued for trial participants. 1 participant who withdrew from the trial declined participation. 26 trial participants took part of which 7 had withdrawn from treatment. Due to low numbers of people who had declined the original trial responding, it was not possible to undertake the analysis.

6.5.5 Discussion

This sub-study was set up to try to determine if there were personality differences between people who took part in the trial compared to eligible people who declined the trial. However, the incentive of offering a £20 gift voucher did not lead to sufficient numbers of people who previously declined the trial from taking part. It would not be suitable to analyse this data when there are insufficient numbers in group 2.

6.5.6 Summary of results

The failure to recruit sufficient numbers to group 2, reveal how some people are reluctant to participate in research, even if offered financial compensation. It again leads to the question about whether the participants who take part in clinical trials are reflective of the general population.

6.5.7 Interpretation of results

It remains difficult to establish how generalisable the results are to the patients outside of trials who experience side effects with statins.

6.5.8 Limitations of results

This sub-study demonstrates that it is difficult to access participants who decline a trial to determine why they declined and raises the question of general bias in clinical trials because many participants decline participation. Face-to-face recruitment could be more useful in understanding non-participation as unlike a mail out, where non-

responders reason for non-responding is a mystery, in a face-to-face situation it is natural that having a face-to-face interaction and social etiquette will more likely evoke a quick explanation by the patient as to why they do not want to take part.

6.6 Summary of chapter

Chapter six demonstrates that follow-up care is important for statin users. Recommendations from health professionals may be thwarted by contradictory information from other people or the media that statins are harmful. Participants say they attribute side effects to statins if symptoms occur when a statin is started, or symptoms stop when they stop the statin.

Chapter 7 will summarise the results of this thesis and interprets the overall results, limitations and recommendations for future practice.

7 General discussions and conclusions about N-of-1 trials in clinical practice

7.0 Chapter overview

Following on from the results presented in the preceding chapters, their interpretation, implications, limitations and recommendations will be discussed. Interpretation of the trial includes preliminary feedback from a patient and public involvement (PPI) group.

7.1 Summary of results of this thesis

7.1.0 Thematic synthesis

The summary of the literature in Chapter One demonstrated that statins are an effective way to reduce serum LDL cholesterol and to lessen risk of cardiovascular events and mortality in both primary and secondary prevention of CVD. Despite statins proven benefit and availability many people discontinue taking them often as a results of side effects. This leads to increased healthcare costs, distrust in the healthcare system and impaired quality of life. Side effects rates in randomised placebo-controlled trials of statins are consistently equivalent to the corresponding placebo arms. Furthermore, in patients who are unblinded or who are taking statins outside of a clinical trial, side-effects appear more commonplace, and this suggests that side effects are either unrelated to the statin or are caused by the psychological act of taking a tablet rather than the statin itself.

The literature review in Chapter Two identified multiple studies where the nocebo effect was induced in healthy volunteers, through both conditioning and expectation. The existing literature shows the nocebo effect to be associated with negative emotions, somatisation and autonomic nervous system arousal. Expectation of side effects and increased perceived risk appear to be associated with the nocebo effect. Studies are limited, but there is some converging evidence that awareness of the nocebo effect may reduce its magnitude. Chapter Two concluded by proposing a testable model for the mechanism of the nocebo effect and proposed based on this theory a line of argument as to why nocebo awareness might reduce the magnitude of the nocebo effect. However, it also predicted that a learnt nocebo effect as opposed to one developed through negative expectation might be more persistent and harder to extinguish. More research is needed to determine if the precedence to the nocebo effect alters level of resistance to its extinction.

7.1.1 Validation and testing of the phone application

Chapter Three gave an overview of the methodology of the trial. It overviewed amendments to the trial protocol and other amendments which largely reflected challenges of recruitment.

In the SAMSON trial a specially designed phone application was developed to measure adverse symptoms with statins. Chapter four gave an overview of the phone applications development and testing. Data were presented to support the applications reliability and validity. Participants completing it felt it was quick and easy to complete. Exploring what people thought about when rating on the app, was reassuring, because there was a consistent and shared understanding of the meaning of 'symptoms' which was in line with how the research team aimed for the app to be perceived. Further to this, the app correlated with constructs of side effects as well as quality of life which suggests it is likely to be measuring adverse symptoms and not some other construct such as anxiety which is also known to correlate with the nocebo effect. In summary, early indications are that the app is a valid and reliable measuring tool for assessing adverse symptoms.

7.1.2 SAMSON trial results

The SAMSON trial results were reported in Chapter Five and showed that in a sample of participants who had previously completely stopped statins due to intolerable symptoms, the majority of adverse symptoms were not likely to be pharmacologically related. The results show an intervention of this type is safe and led to no serious adverse events. 50% of the trial participants restarted a statin 6-months after the end of the trial.

7.1.3 Qualitative Study of experiences of statins and side-effects

Chapter Six used qualitative interviews to explore people's experiences of statins and in some cases side effects with statins. The interviews included participants who were not willing or ineligible to participate in the SAMSON trial. Furthermore, it gave information about the context of the trial's recruitment and what elements or processes may have influenced the trial results. In the interview study, participants valued regular follow-up with health professionals about their progress with statins. Patients sometimes spoke of impasses when they had suspected side effects with statins because prescribers were reluctant for them to stop statins. Statins do not provide any explicit symptom relief and so success of statins is judged by individual participants in various ways, commonly by reduction in cholesterol or an absence of a cardiovascular

event. Some participants spontaneously discussed the SAMSON trial and said it could help to resolve the question of side effects.

7.2 Interpretation of results

7.2.0 Thematic synthesis

The review in Chapter Two, suggests that awareness of the nocebo effect may reduce the nocebo effect from developing because it allows participants to interpret and attribute adverse symptoms to the nocebo effect. Whereas, if a person is unaware of the existence of this phenomenon they would not be able to alleviate their anxiety about the adverse symptoms they are experiencing because they have no alternative explanations of their symptoms.

7.2.1 SAMSON trial results

In terms of the trial, in line with the hypothesis 1, greater than 30% of participants enrolling completed it. 82% of participants actually completed the trial. Consistent with hypothesis 2, greater than 50% of symptom burden was nocebo rather than pharmacological; there was no significant difference between the mean score for placebo and statin but there was a significant difference between no treatment months and tablet months. In line with hypothesis 3, the majority of participants at 6-months were either taking a statin or had declined it for reasons other than perceived side effects.

These results help explain the paradox of no difference in symptomatic side effects between statins and placebo in the 80,000 randomised controlled trials participants,(Finegold et al. 2014) despite side effects being the commonest reason for clinical statin discontinuation.

One possible origin for statin side effects is a direct pharmacological effect on tissues. Statins are intended to interfere with liver metabolism, reducing cholesterol production. Placebo-controlled trials show that statins do elevate blood levels of liver enzymes, but do not show elevated symptoms until the participant is unblinded and discovers they are taking a statin. A second possibility is that patients starting statins may notice a chance increase in background symptoms, and correctly note they have increased. A third possibility is unintentional creation of a false association through patients or doctors trying to test causation by starting and stopping tablets as an informal experiment. Unfortunately, without a pre-planned schedule, the statin tends to be

stopped when symptoms are maximal (and naturally tends to decline) and are restarted when symptoms have resolved (and can only get worse). These informal experiments replace uncertainty with confident, incorrect conclusions, and therefore may be problematic. Fourth, patients may be primed to expect symptoms. Sources of negative suggestion include media and Internet coverage and side effects listed in leaflets (that conventionally do not compare active with placebo). Even a clinician responding to symptom reports by changing the dosage, frequency or agent, might reinforce a patient's belief that the statin was the cause of the symptom. A fifth explanation is that patients previously had true pharmacological side effects with a statin and this has primed a nocebo effect even when participants took placebo tablets in the trial.

SAMSON did not find any evidence of the first possibility, a direct symptomatic effect of the statin. The second possibility is eliminated by documenting symptoms frequently and contemporaneously, via a symptom app. The third possibility of artefactual association by reverse causation, is eliminated by the pre-arranged schedule. The fourth possibility is tested by having *both* no-tablet *and* placebo tablet arms, which reveals the expectation of side effects to be the dominant contributor, since symptoms are much worse on placebo tablets than no tablets ($p<0.0005$), and there is no difference between placebo and statin ($p=0.499$). The fifth explanation is at least slightly discounted because some patients restarted the same dose of statin they were previously on and encountered no symptoms.

The day-by-day individual participant symptom scores reveal a variety of patterns. Some (e.g., participant 1053) had few symptoms, others (e.g., 1010) had frequent symptoms throughout, and others had intermittent symptoms, but only when taking tablets (be they statin or placebo, e.g., 1045).

24 patients (on 71 occasions) had symptoms so severe as to stop tablets early, demonstrating symptoms as distressing. However, this rate was the same between statin and placebo. This shows the cause, in some cases is taking the tablet, and not the biochemical effects of the statin.

Prompt recovery from symptoms after stopping tablets is often interpreted by patients and clinicians as evidence of causation. Our data indicate that this is true, but because the recovery kinetics are identical between placebo tablets and statin tablets the causation is from taking a tablet, rather than from the tablet being statin.

Participant 1043 was the only participant who had symptoms only on statin months however, it might be expected that purely by chance, a participant could randomly have statin months with symptoms.

The three-arm n-of-1 design (including no-tablet and placebo periods) allows individualised verification of the existence of side effects on statin tablets, and exploration of the contributions of taking a tablet and the tablet being a statin.

N-of-1 trials may be beneficial for people in the future where the causality of side effects is unclear and may reduce the perceived threat of statins if it can be shown that side effects are equivalent in the placebo condition. It also may be helpful to eliminate a statin as a cause of symptoms if people are on multiple medicines or have other health conditions. However, there is potential for unexpected effects of the trial such as it to shift the nocebo effect to another medicine, one participant commented when he received his results *'oh it must be my beta-blocker then!'* so indirect consequences of the trial will need to be carefully assessed in future research. N-of-1 trials are a potential intervention for people who have suspected statin side effects, but it may also be useful to undertake research on whether there are any benefits to informing people of the nocebo effect to allow them to consider an alternative way to attribute causality of symptoms, as causality cannot be attributed to something else if a patient is unaware of its existence.

After the trial results were published one of the National Heart and Lung Institutes PPIs group were asked to give feedback on the trial and results. They were given a short summary about the trial and asked to give their views of the SAMSON trial and the results and it was highlighted there was no wrong or right answers. The PPI group comments are shown in Figure 33.

Positive views of the trial:

'Yes. I am someone who pays attention to the views of experts in medicine. Research is important and valuable. If research shows that statins are valuable in reducing harmful cholesterol and they cause no harmful side effects I believe patients should take them if prescribed by an expert. If research shows that some people believe that a placebo causes side effects it should be explained to the patient that this is a psychological response which is not evidenced by research and facts'.

'I think trial is important and the results are fascinating. The results feed my prejudice of the power of psychology and influence'.

'I understand that far too many people choose not to continue to take medication prescribed and this (the trial) appears to indicate one reason why this happens.'

'I would wish to know if I had 'imagined' I had suffered side effects (if that were the case) so that I could understand my own psychology'.

Negative views of the trial:

'I think that the stated conclusion is possibly premature – as was said in the report the issue of side effects is complex – so more controlled trials suggested'

'Yes – needs more explanation of the calculation of the proportion of symptoms directly attributable to statins and what the rationale/evidence for this attribution is'

Figure 34: PPI group views of the trial results

The results are from one PPI group but indicate a positive view of the trial and it's results and utility. It also highlights that some people may be sceptical of a definite conclusion being drawn from such results and this may explain why some trial participants did not restart a statin despite results suggestive the statin was not the cause of their symptoms. Also, PPI members highlighted people may want to understand how their scores were calculated, which was reassuring as this was undertaken with participants as part of the result-giving visit during the trial.

7.2.2 Qualitative Study of experiences of statins and side-effects

Discrete events appear to influence a person's view of statins effectiveness such as a cholesterol result or a cardiac event. If a person has a cardiovascular event while taking a statin they might deem them as not effective. Furthermore, other peoples' experiences appear to influence people's views and expectations about statins. Media stories, patient information leaflets and conversations with friends are just some of the ways patients can start to form negative expectations of statins which they might then consider relevant to themselves.

Time spent with, and trust in, the prescribers might allow concerns and misunderstandings to be more readily resolved. Regular follow-up is something that participants value and might be useful if patients are continually being exposed to conflicting information. Again, lack of awareness of the nocebo effect might also be an issue, if adverse symptoms are only attributed to statins as patients are not aware of anything else that could plausibly lead them to have symptoms.

This study shows, despite prescribers being highly regarded sources of information, there is substantial information in the public domain such as newspaper reports and

acquaintances that contradicts the credibility of the evidence-based advice given by prescribers. Therefore, prescribers may face hidden challenges when recommending a statin due to other information the patient has been exposed to and it may be necessary for prescribers to identify and resolve any dissonance. The nature of a patient's self-management of cardiovascular disease may give indications to healthcare staff about how they view the efficacy of treatment and what other sources of information have influenced the patient's view.

If a patient believes they have had side effects with statins, prescribers should be mindful of the way they address this issue, to avoid the patient feeling their views have been dismissed or not regarded as legitimate. Whatever the cause of the adverse symptom, for the patient the adverse symptom may represent substantial distress and currently patients' need for emotional support from prescribers might sometimes be going unmet.

Patients may associate a statin with an adverse symptom if it occurs at the same time as the statin is started or if the symptom stops after a statin is stopped. Patients appear to consider polypharmacy to increase their risk of side effects. Some participants are unclear about the cause of adverse symptoms and are open-minded to the possibility of a nocebo effect, but the nocebo effect appears not to be a well-known concept among most patients.

If side effects occur, patients are more likely to persist with statins if they perceive the side effect is not a great threat to their wellbeing or if they are concerned about their cardiovascular risk. However, some participants are unaware that even without optimal cholesterol lowering, statins still have benefits for the prevention of cardiovascular disease. Hence, some patients may stop statins because they have minor side effects and are unaware of the CVD risk reduction they are still getting despite their cholesterol level not being optimised. Participants whose side effects had direct or indirect threats to well-being or that were seen as inhibiting activities of daily living, discussed stopping or being told by prescribers to stop statins as a result.

7.3 Implications of results

7.3.0 Thematic Synthesis

This review found that conditioning, expectation and suggestion might be influential in the nocebo effect. In another review (Wolters et al. 2019) verbal suggestion and conditioning together was shown to evoke pain. Whilst, conditioning was shown to

evoke nausea and breathlessness. Expectation also evokes breathlessness and itch but not fatigue or nausea. Another review has highlighted the importance of patient-clinician communication and the importance of disclosure of the nocebo effect (Colloca and Miller 2011). The review in Chapter Two has gone beyond existing reviews, by proposing a testable mechanism by which nocebo awareness might attenuate the nocebo effect. This review proposes that more research is needed, to understand if it is beneficial to inform patients about the nocebo effect.

7.3.1 SAMSON trial results

The results have important implications for patients and physicians when symptoms are experienced on statin tablets in routine clinical practice.

The first practical implication is that even severe, convincing and intolerable symptoms in clinical practice sometimes do not reappear on formal evaluation with daily documentation. This occurred in participants 1011 and 1053 who had each previously abandoned statin regimens.

Second, formal documentation of symptom scores sometimes reveals the culprit to be background fluctuations in symptom intensity, regardless of tablets (e.g., participants 1010 and 1060).

Third, there is undoubtedly a clear verifiable side effect of statin tablets. However, these were identical in intensity between statin and placebo, which means that even reproducible symptoms on statin tablets give a clinician no information about whether the statin in those tablets is the cause.

Fourth, it is wrong to interpret rapid symptom decline after stopping tablets as evidence that the statin was the cause, since the decline is similarly rapid and profound for both statin and placebo.

In conclusion, side effects from taking statin tablets are verifiable, but are driven by taking tablets rather than by the tablets containing a statin. The cues and informal experiments patients and clinicians use to test causation can paradoxically confirm a non-existent association. This error is prevented by a scheduled, three-armed, n-of-1 trial containing no-tablet periods.

The cost of producing the medicines for the SAMSON intervention was approximately £510 per participant. 50% of patients restarted a statin after the intervention. The acute costs alone of treating a myocardial infarction first event is estimated to be £4275 (Danese et al. 2016). So, the intervention is likely to be cost-effective.

Statins are commonly prescribed and receive a lot of media attention. For example, the results presented in Chapter Five were presented at the American Heart Association conference and published in a letter in the New England Journal of Medicine. On the day of publication, it was widely reported on in the UK mainstream media with articles in the Guardian, Daily Mail, Telegraph and BBC News (see in Appendix 23). At one point on the day of its publication it was the most widely read story on the BBC News Online app. What is more, statins do not alleviate symptoms and so their benefit is 'silent'. With widespread negative information about them and irregular positive feedback, patients might be more prone to develop negative associations about statins.

The SAMSON trial results are the first n-of-1 trial of statins, which used no tablet periods. It builds on existing evidence from the literature about the existence of a nocebo effect or psychological aversion to tablets and raises the question as to how far reaching the nocebo effect is in medicine and it is something that needs to be better understood with further research on the phenomenon. The results show no overall difference between symptoms between statin and placebo arms and is consistent with other trials of similar design (Joy et al. 2014, Herrett et al. 2021).

The results do not fit with the current management of statin therapy and indicates a need for a review of current management practices. Inf light of the findings in this thesis, the existing management by physicians might be potentiating the nocebo effect and even conditioning the nocebo effects. There appears to be a lack of awareness of the influence of the nocebo effect among health professionals and patients. Therefore, as well as assessing the effectiveness of drugs, more is needed to be learnt about the psychosomatics of taking a drug. Further, it may prove important that patients are informed of all side effects not just pharmacological ones as they are often equally distressing. The review in Chapter Two suggests informing about the risk of the nocebo effect might help prevent it, but more direct research is needed. In light of the findings in Chapter Two, interventions to alleviate negative associations with healthcare might be useful to explore to determine if for example a friendly approachable physician, an on-time appointment or calming music in the waiting room might reduce the risk of a nocebo effect.

The SAMSON trial provides a new insight into the relationship between taking a tablet and the nocebo effect. These results should be taken into account when considering how to assist patients with restarting a statin and the awareness of the study and its findings potentially could itself give confidence to patients to restart a statin. Misattributing statins as the cause of side effects would seem only natural when patients are not even aware of the existence of the nocebo effect and so are unable to attribute the act of taking a statin with anything but the pharmacology of the drug. This is further reinforced by the drug information leaflets which will likely list the adverse symptom a person is experiencing as being a potential side effect of the drug without clarifying the equivalent rates of the side effect in the placebo groups nor warn of the risk of the nocebo effect as a possible side effect on the drug information leaflets.

While previous research has focused on if statins are harmful, these results demonstrate that the act of taking a tablet is harmful. statins appear vulnerable to the nocebo effect possibly because they are a very commonly prescribed drug, as such they attract a lot of attention in the media, and they provide no explicit symptom relief. The trial results raise questions about whether more should be done to help patients envisage the benefits of drugs like statins where patients do not necessarily get frequent measurable benefit. Measurement of cholesterol levels alone may in some cases demotivate patients because reduction in LDL cholesterol is not as much as expected.

This thesis demonstrates the nocebo effect is real and can be induced in most people under the right conditions. Importantly, a well-designed intervention to measure the aetiology of side effects with statins, appears to effectively help people to restart a statin.

The results show the intervention is very effective at helping people to restart a statin, but further studies are needed with longer follow-up periods to understand if this type of intervention would work outside of a trial setting. It appears also that participants interviewed stated that they valued regular follow-up about statins. Future studies need to pick apart what aspects of the SAMSON trial made it successful. Did providing participants evidence about their individual symptoms contribute the most to its effectiveness or was it regular follow-up with trial doctors or as simple as informing people in general about the existence of the nocebo effect?

7.3.2 Qualitative Study of experiences of statins and side-effects

Previous literature is limited. One study has shown general practitioners considered patient attitude to primary prevention and negative media coverage had an impact on adherence to statin therapy, they considered barriers to overcome by combining motivation and education with person-centred care and used individual computer programmes for communicating risk-benefit analysis (Dunne et al. 2014). Our current study demonstrates patients are also in a dilemma in terms of weighing the importance of information they get from various sources and therefore may disregard or mistrust medical advice.

Interview studies exploring patients experiences of statins are limited. One interview study has explored side effects with statins to explore which activities of daily living (ADLs) were effected by side effects (Vrablik et al. 2019). Our study suggests that if ADLs are inhibited by experienced side effects participants may stop taking statins.

Negative statin-related news stories are associated with cessation of statins (Nielsen and Nordestgaard 2016). The qualitative study in Chapter Six demonstrates how negative news stories and information from other sources can undermine and plant doubt in patients' minds about the medical advice they are given.

A survey of statin-related adverse symptoms identified that the most important reason to continue statins was to avoid MI, stroke and to lower cholesterol or because a doctor recommended them. Being bothered by side effects was the most common reason to discontinue statins (Jacobson et al. 2019). Furthermore, in those who discontinued, the severity of the adverse symptom was higher than in those who continued statins despite symptoms. The results in Chapter Six showed that participants who were very concerned about their cardiovascular risk persisted with statins despite perceived side effects and those who perceived a greater threat to their well-being from side effects stopped statins.

7.4 Limitations

7.4.0 Thematic synthesis

This review has generated a testable theory, but it is as yet untested and only based on a limited number of studies. However, the theory can be used to design further studies to test it. Also, further published studies on the nocebo effect could refine it further.

Limits were placed on the number of included papers due to the resources available to the research team. Every effort was made to identify all papers, then exclude lower

quality ones whilst still determining none of the excluded papers covered an area not explored in the papers included.

The method is not traditional. However, nocebo literature is in its infancy and so this type of review may help conceptualise the current literature and look at directions for future research.

Limitations of using qualitative studies and empirical studies are that they may not reflect the nocebo effect in clinical practice. People in a research experiment may be more confident that they will not come to harm and many of the healthy volunteers were in their twenties so do not reflect the ages where medication are taken for chronic conditions and patients are more likely to have co-morbidities. Most of the papers looked at nocebo hyperalgesia, so this proposed theoretical model might be less relevant to other types of nocebo symptoms. However, this review proposes a testable theory that can be explored in future research and nuances can be explored and used to further refine the theory.

7.4.1 SAMSON trial results

The generalisability of the trial results is limited by it being a small sample of participants from one site in one country. However, its homogeneity means its method was consistent between each participant enrolled and can be easily repeated in different samples to see if the results can be replicated across different contexts.

The intervention involved regular support from health professionals and this may have been influential to patients restarting a statin. Future interventions would benefit from testing the individual components of the intervention to determine whether it was giving results or support or awareness of the nocebo effect that was most instrumental in the restarting of statins by participants. Participants entering the trial may have been more motivated and had more intention to restart a statin than people who declined the trial, so the fact only 50% restarted a stain could be viewed less positively. However, for ethical reasons the trial avoided recruiting participants who were still taking statins despite side effects. Therefore, patients enrolled in the trial were only participants who had prior to the trial abandoned statins altogether and had no plan to restart them, so in reality they may have been more resistant to restarting a statin. In Chapter Two, expectation was shown to be influential in terms of the nocebo effect. Possibly those who were willing to enrol in the trial, were more open to the expectation that their

results would show a nocebo effect whereas those declining the trial expected their side effects were statin related and would have therefore been less willing to restart a statin after the trial. There was a large proportion of people who declined to take part and in these groups the intervention might not be so effective. Eligible patients who declined the trial, were also invited to take part in the personality sub-study which involved completing a simple 1-page questionnaire for which they were offered a £20 gift voucher. Despite the simplicity of the sub-study and the financial incentive only 5 people responded, indicating the trial intervention itself may not have been the main cause of non-response but rather an aversion to research generally. However, even if the intervention is not generally well-received, it is a useful option for statin users with side effects who are motivated to test for themselves the causality of their symptoms, even if it is still useful for only a minority of patients, it still is potentially an effective intervention, but one-size may not fit all when it comes to interventions for overcoming the nocebo effect. However, if the intervention could eventually be rolled out in clinical practice such as in GP practices or lipid clinics, participants who would opt-out of research might eventually still opt-in to a well-recognised clinical intervention.

Due to the majority of symptoms being myalgia in the trial it is not possible to determine if certain nocebo symptoms are more amenable to this type of intervention, but this is something that should be explored in future studies. What is more, the app could potentially be developed to measure each individual symptom separately to explore differences in symptoms further. The app used in the trial might be further standardised by changing '*no symptoms'* up to '*worst imaginable*' instead to '*no symptoms'* up to '*symptoms severe enough to stop taking*'. It would appear participants assessment of what worst imaginable or a score of a 100 might be is very extreme symptoms yet a score much lower than 100 was severe enough to make participants stop taking their tablets. Therefore, people might more consistently rate in the same way if asked about what level of symptoms would make them stop. g. Symptoms that made patients stop were looked at qualitatively between statin and placebo months and there appeared to be similar symptoms reported between placebo and statin months, but more research is needed to confirm this.

The trial used treatment blocks of 1-month, and the eligibility criteria excluded participants whose side effects took longer than 2-weeks to onset. Therefore, the

study's results are limited to more rapid onset symptoms. Further research trials with longer treatment blocks could determine whether patients whose symptoms take a greater time to onset are more prone to 'true' pharmacological effects or if these are likely to be more prevalently nocebo effect. Elderly patients greater than 80 years old were not represented in the trial. This population has physiological changes from age and a greater number of co-morbidities, future studies would be useful to understand aetiology of statin side effects in this group and whether true side effects are more prevalent or not (Horodinschi et al. 2019). Furthermore, the SAMSON trial did not collect data on physical activity and intensity and this might be important to explore in future trials in terms of symptoms such as myalgia.

Some of the methodological choices were constrained by funding, it would have been preferable for the study team and participants to be blinded to the results until all participants had completed the trial, but enrolment in the trial was over several years, so it would have been unethical to withhold and delay giving individual results when this information might lead to a participant restarting a statin. Future trials could attempt to recruit all patients in close succession, so results can be revealed to participants after all participants have completed the trial. However, in terms of this trial, it is unlikely that participants who were active in the trial had contact with participants who had completed the trial and shared results. What is more, the study team always remained completely blinded to treatment order until a participant completed all 12-months of the trial. As such it is unlikely the study team could behave in a biased way to participants still on the trial as every participant had an unknown order of treatment.

The deviation from the statistical analysis plan was another limitation of the trial. The analysis proposed in the first version of the protocol was the basis for the statistical analysis plan but a deviation was required because the data did not meet the assumptions that were expected. The statistician completing the analysis was independent and also performed the analysis in the original statistical analysis plan and it was explicitly stated about the deviation and reasons for it in the first published results paper and the protocol was updated to reflect this. As this was the first trial of its kind, that used no tablet arms as well as placebo and statin, there was no established way to analyse the data. Now the trial results have been published, future

researchers have the benefit of a pre-specified approach to statistical analysis, if they attempt to replicate the trial.

The primary endpoint for nocebo effect deviated from the planned analysis in the statistical analysis plan (SAP). However, this was because the trial statistician had remained blinded to the data when writing the SAP and it was only during the analysis a statistician was unblinded to the results and noted the data violated the assumptions. This is the first trial of its type, no other n-of-1 trial with statins has used a no treatment arm and so the data pattern was not foreseen.

The generalisability of the results is limited by it being a single site trial, however participants did come from around the UK. Every effort was made to record of those invited who declined or who was not eligible. Still, it might be possible that some participants who declined the trial had more severe adverse symptoms than those who took part.

The methodological choices were constrained by ethical considerations. It would not have been in the best interest of patients to stop a statin if they were tolerating it despite symptoms. So only patients who had completely stopped statins were recruited. What is more it was impractical for the first trial to have included participants whose onset to symptoms took longer than 2 weeks to appear because of the need for much longer treatment blocks and commitment to the trial. Therefore, it was appropriate to undertake the first trial in participants with whom the treatment blocks could be as short as possible, but this could be expanded in future trials now the trial has been shown to have utility.

After the trial, 50% of participants restarted a statin, but it could be argued the literature suggests re-challenging with a statin is often successful. However, arguably these participants were beyond the point of rechallenging with a statin as before the trial they had already decided to permanently stop a statin and so it is reassuring even in this group 50% could be convinced to restart a statin.

7.4.2 Qualitative Study of experiences of statins and side-effects

There are several limitations with this study, the number of participants interviewed was relatively small, and although thematic saturation was reached it could be this was due to the limited diversity of participants that were interviewed. However, the

interviews involved exploring the views of people with a range of different experiences of statins and allowed further insight into the patient's experience of taking a statin.

7.5 Recommendations

7.5.0 Thematic Synthesis

The findings have important implications, firstly, the nocebo effect appears to be a major cause of side effects in certain disease conditions, yet there appears to be relatively little research conducted on it. It appears important for health professionals and patients to be made aware of its influence, but more research is needed to establish this with more certainty. Secondly, as with gambling, partial reinforcement of the nocebo effect could potentially lead to a harder to extinguish nocebo effect. Patients who have transient symptoms that coincide with treatment, could be learning to associate an effect between the treatment and adverse symptoms which are truly unrelated, and more so because they are unrelated or partial. More research is urgently required to investigate this phenomenon further. The findings of the review definitely suggest that making patients and health professionals aware of the nocebo effect is an important avenue to explore in terms of reducing or preventing the nocebo effect. What is more, arguably, if the nocebo effect is such a prevalent side effect for patients then its' risk when starting a therapy should be communicated to prevent harm and to limit patients discontinuing an effective therapy.

Further empirical studies need to be undertaken to determine if awareness of the nocebo effect does attenuate its effect. If evidence demonstrates this is effective, major changes to training of health professionals needs to be undertaken so this sort of communication becomes commonplace in clinical practice. Furthermore, in terms of research about the nocebo effect it is useful to understand what the common nocebo side effects are and what are the most influential risk factors for the particular side effects, so interventions to prevent them can focus on these key risks.

7.5.1 SAMSON trial results

Future research should address why statins show such a high nocebo effect. One possibility is statins commonly being started for primary prevention where there are no symptoms to improve, and in an age group in whom ill-defined discomfort becomes increasingly common. In light of Atorvastatin being the most prescribed medication, (a) there are more patients to make an initial report of symptoms, (b) media, appropriately, have a greater interest in publicising them, and (c) individual readers

have a higher probability of being on the drug and having their attention drawn to symptoms. This triple combination might explain the dramatically higher public perception of side effects with statin tablets than with other medications.

Further research is needed to establish the cost-benefit of performing n-of-1 trials within the NHS for individual patients who have experienced side effects.

When a patient starts a statin, the prescriber must use effective ways to inform patients about the drug and its purpose. Regular and repeated access to support from health professionals after starting a statin appears to be preferential. Conflicting information about statins appears to lead to confusion and concerns in patients about statins. Information for patients to better critically appraise sources of information and separate fact from opinion might be useful to help patients to better critically appraise sources.

7.5.2 Qualitative Study of experiences of statins and side-effects

Table 17 summarises recommendations based on the results of the qualitative interviews in Chapter Six.

Table 16: Subthemes with suggestion for practice subthemes with authors' suggestion form practice

1. Management of statins	
Understanding of CVD, risk perception and its treatment	Confirm patient is aware of the wider goals of statin therapy, not just cholesterol lowering
	Confirm patient is aware of need for long-term use of statins
Professional communication, support information and trust	Prescribers are sensitive to a patient's belief in side effects
	Prescribers make clear their motive for prescribing statins
	Determine which other sources of information about statins patient have been exposed
Follow-up and continuity of care	Establish a patient's preference for evaluation and feedback whilst taking statins
	Establish if there any issues the patient is having with their current prescription of statin
Perceived efficacy of statins	Perceived efficacy of statins might be questioned if cholesterol does not reduce or if patient has a cardiovascular event whilst taking a statin

Self-management/Self-efficacy of CVD	Types of self-management being used, such as weight management, diet, exercise and self-research about their conditions might indicate other sources of information about statins the patient has been exposed
	Perceived lack of efficacy of statins may increase self-management of CVD
	2. Experience of side effects
Causation of side effects	Factors associated with attribution of side effect to statins:
	Adverse symptoms occur at around the same time a statin is started
	Adverse symptoms stop at around the same time as a statin is stopped
	Other medicines are ruled out as cause of adverse symptoms
	Information for internet, patient information leaflets (PILS), other people's experiences
	Polypharmacy
	Lack of awareness of the Nocebo Effect
Sources of information about side effects	Common sources of information include internet, PILS, other people's experiences
Consequences of side effects	Factors associated with stopping statins due to side effects:
	Perceived threat to well-being
	Inhibit activities of daily living
	Worsen pre-existing emotional distress
Perseverance with statins with side effects	Facilitators of persistence with statins:
	Adverse symptom causes only minor perceived threat to well-being
	Adverse symptom does not inhibit ADLs greatly
	Change time of day of taking statin
	Change to a different statin
	Treat adverse symptom
	Symptoms do not persist
	Perceived threat to well-being if does not take statin

7.7 Conclusion

Statins have already been well-proven as an effective way to prevent and manage cardiovascular disease. The SAMSON trial results demonstrated there was no

significant difference in symptoms between statin or placebo tablet months but there was a significant difference between tablet and no tablet months. What is more, after being given their personal trial results 50% of participants restarted a statin. The results offer a promising and safe intervention to help patients restart statins. This type of intervention also has potential utility for other drugs where nocebo is suspected to be an issue. Furthermore, the research explored individual experiences of statins and found that although there is trust in medical professionals there is a lot of counter-information about statins that can make people unsure what to believe. This thesis demonstrates there is little research about the nocebo effects impact in clinical practice despite it appearing to be quite influential to many patients and can lead to life-saving treatment being stopped. Making patients aware of the nocebo effect might be another potentially cost-effective way for preventing or reducing the nocebo effect, but further research about this is required. This research reflects that current management of suspected side effects might not be effective or even counterproductive and calls for review of current guidelines in light of the results of this thesis.

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Appendices

Appendix 1: CASP ratings of randomised controlled trials was undertaken by two separate researcher discrepancies were discussed and resolved.

Author	Question number	FW score	MF score	Description of discrepancy
Aslaksen et al. 2015	1	2	1	MF commented 'we're not blinded to hyperalgesia suggestion which is the main interest of the study' But FW comments 'hyperalgesia suggestion' is intervention they are not aware of the effect this intervention is

				supposed to have on them so therefore they are blinded.
Aslaksen et al. 2015	10	1	2	MF no limitations. FW said limitation was 'Yes, pain was the important outcome - state anxiety could have also been considered'
Colagiuri et al. 2015	10	1	2	MF 'Yes all clinically important outcomes. FW :'Yes, limitation not tested for longer to see if extinction'
Crichton and Petrie 2015	6	1	2	MF said ' all accounted for' FW ' States 66 participants randomised, does not state regard any exclusions prior to randomisation'
Crichton and Petrie 2015	10	1	2	MF said, 'Yes all clinically important outcomes considered' FW 'It would have been interesting to understand participants baseline views about wind farms and whether this differed between groups, but both reacted similarly to session 1.'
Harvie et al. 2015	2	2	1	MF 'each subject was own control' FW 'within-subjects, randomized, double-blinded, repeated-measures design' FW 'within subject is a valid design when intervention effect is transient and within subject reduces variance'
Harvie et al. 2015	3	2	1	FW 'Double-blind' MF 'Described as double blinded. However, each patient would be aware of rotational gain effect. More like single blinding' 'FW suggests wearing VR mask stopped them being aware of rotational gain'
Harvie et al. 2015	6	1	2	FW 'Does not state number of excluded, although states there were excluded participants.' MF ' All accounted for'
Jacobs and Schagen 2017	1	1	2	FW: Quite broadly...Building on nocebo and stereotype threat literature, we extend previous findings in three specific ways, by investigating (a) risk factors; (b) underlying mechanisms; and (c) an intervention to reduce AIE' MF 'considered focused'
Jacobs and Schagen 2017	2	1	2	FW 'Yes (was randomised) but baseline characteristics were not verified, or controlled for, not clear if randomised groups varied at baseline.
Jacobs and Schagen	Is it worth continuing	No	Yes	If MF agrees regards 1 and 2 then confirm agreement with not continuing – as 2 or less
Peterson et a. 2014	2	2	1	MF ' Each patient was own control' But FW 'open vs hidden' was randomised
Roderigo et al. 2017	10	1	2	MF 'yes' All clinically relevant outcomes considered. FW commented : 'Of 219 screened, only 120 randomised, it would be useful to determine reason for non-inclusion and if people declined the protocol to compare their baseline characteristics and trait anxiety etc with those who agreed to participate, as the intervention itself might be a cause of stress for some participants and so decliners might have different characteristics and the characteristics of those

				participating might be confounded by a characteristic that also makes them willing to participate.'
Verrender et al 2018	3	2	1	FW ' double-blind' MF Said, 'Blinded in some aspects of experiment'. FW 'I believe as in a previous study, you consider the video is unblinded, I would suggest it is an intervention and it is blinded as participant is not aware of different effect that is hoping to be achieved from different videos'
Verrender et al. 2018	10	1	2	MF said 'Yes' all clinically important outcomes considered. FW ' It may be useful to have RF-On and RF-Off as well as sham Ron and Sham RF off'

Appendix 2: Original SAMSON trial protocol

Study Acronym: SAMSON

Study title: Self-Assessment Method for Statin side-effects Or Nocebo (SAMSON) trial

Version 1.0 Dated 6th September 2015

Funder:	The British Heart Foundation.
Sponsor:	Imperial College London
Protocol Number:	1.0
EudraCT Number:	2015-004109-18
FUNDER:	British Heart Foundation
Product:	Atorvastatin
Development Phase:	IV
Protocol Date:	6th September 2015

This protocol describes a participant-empowering within-subject randomised controlled trial and the development of a practical technology to support 21st century primary prevention decisions and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. This study will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Study Management Group

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Clinical Queries

Clinical queries should be directed to Dr Judith Finegold who will direct the query to the appropriate person.

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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1 INTRODUCTION

1.1 BACKGROUND

Cardiovascular disease remains the main cause of death world-wide[1,2,3,4] despite advances in medical therapy[5,6,7,8,9,10]. Highly effective preventive regimes are available, but adherence is poor[11,12,13,14,15] . There are many causes of non-persistence with medication[16]. Many participants who have indications to receive preventative medication see it as only appropriate for the sick, and – not seeing themselves as sick – seek to avoid medication[17,18]. Non-adherence tends to be higher with poor health literacy, lower socioeconomic class[19] and increasing age[20].

Statins reduce cardiovascular event rate by a large proportion[21,22,23] but many participants outside trials do not persist with therapy, often because of adverse symptoms that they attribute to the medication. Growing societal suspicion of high adverse event rates in real-life experience is now discouraging even first-time initiation of therapy.

When an adverse symptom is experienced after initiation of a statin, the clinician has a limited repertoire of steps to take. Commonly the drug is stopped and re-tried after an interval with the participant - quite appropriately - advised to bring any recurrence of symptoms to medical attention. In other cases an alternative statin may be tried, with a similar warning to be alert for recurrent symptoms.

Analysis of the 83,880 participants who have received statins versus placebo in double-blinded randomised placebo controlled trials[24] shows no sign of a tendency for greater adverse *symptom* rate on statins versus placebo, if one sets aside increased glucose which is almost never the symptom stated as a reason for stopping statins.

Just as the placebo effect describes a favourable psychobiological effect following the administration of a placebo, the nocebo effect describes the adverse effect a participant experiences through taking a medication, not due to the medication itself. Previous studies quantified the nocebo effect by measuring adverse drug reactions when a placebo is administered and have reported nocebo effects ranging from 19% to 27%[25,26,27]. The nocebo effect is influenced by many factors[28], but undoubtedly the information a participant is given about a drug modifies their expectations and therefore their response[29]. Conditioning from previous negative experience also strongly influences the nocebo effect[30].

1.2 RATIONALE FOR CURRENT STUDY

Front-line clinicians cannot currently test for an individual participant whether symptoms experienced are the pharmacological result of a statin or due to other phenomena e.g. nocebo. The value of such a tool would be twofold:

- It would allow individual participants to establish for themselves whether they truly suffered a side effect from the drug, or are victims of nocebo - which may in fact be commoner
- By separating the components it would permit clinical researchers to explore the determinants of each, opening opportunities to obtain better outcomes

1. *Hypothesis 1:* that >30% of participants enrolling for the study will complete it.
2. *Hypothesis 2*: Overall >50% of symptom burden is nocebo rather than pharmacological
3. We will define the Nocebo proportion of side effects as shown in Figure 1:

$$Nocebo\ proportion = \frac{Nocebo\ component}{Total\ side\ effect(Pharmacological + Psychological}$$

4. *Hypothesis 3*: that the majority of participants, at 6 months after completion, will either be taking statins or have declined statins for reasons other than perceived side effects.

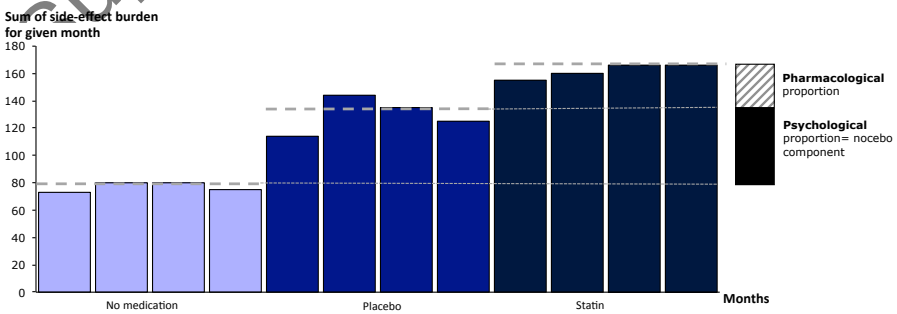


Figure 1: Example of a possible result from a single participant.
Each participant will undergo twelve randomly ordered 1-month periods. There will be four periods of no medication, four periods of placebo and four periods of statin. The placebo and the statin pills will be identical in appearance. Participants will record on a daily basis side-effects experienced.
At the end of the study, the one-month sessions are sorted into the order shown above. The participant can then observe directly how much of the increase in symptoms seen with statin is also seen with placebo.

2 STUDY OBJECTIVES

This project will develop, test and deliver a method for this, in the following stages:
1. We will develop a method for determining within an individual participant to what extent experienced symptoms are associated with the statin or merely nocebo effect
2. We will evaluate in a cohort of participants who have stopped statins because of adverse symptoms, in what proportion of them, the symptoms are truly due to the statin

3 STUDY DESIGN

3.1 PRE-RANDOMISATION EVALUATIONS

A participant and public involvement group have already provided feedback to assist the development of the study proposal. Their feedback is summarised in Appendix 1. The phone application has also been piloted among healthy volunteers and feedback summarized in appendix 2.

3.2 PILOT STUDY: SEMI-STRUCTURED INTERVIEW TO EXPLORE AND MEASURE SYMPTOM EXPERIENCE TO REFINE MEASUREMENT TOOLS FOR THE MAIN TRIAL

Participants: Prior to the trial we will recruit 20 participants who are either 1) currently taking statins with and without adverse symptoms or 2) have previously ceased statin therapy due to adverse symptoms.
Method: The interviews will have two parts. Firstly, we will conduct a brief interview to explore individuals' current or past experience of statins. Secondly, participants will fill out a structured questionnaire that assesses the intensity within each participant of several commonly described statin side-effects, each on a scale of 0-100. These would include muscle aches, fatigue, headache, and gastrointestinal symptoms. In addition, the participants will be asked to complete and comment on the daily and monthly questionnaires planned for the main trial to assess their appropriateness. At the same session participants will have a cognitive interview[31] to determine their reasoning whilst filling out various different scales. The interviews will be audio-recorded and transcribed using Nvivo software. The exploratory part of the interviews will be interpreted using thematic analysis[32] and the cognitive interviews using a content analysis approach[33].
Scale refinement: The scales used in the main trial will be refined based on the findings from the interviews, and any modifications piloted among further participants.

3.3 RANDOMISED CONTROLLED TRIAL: EVALUATING IN A COHORT OF PARTICIPANTS THE PROPORTION OF ADVERSE SYMPTOMS TRULY DUE TO THE STATIN RATHER THAN THE NOCEBO EFFECT

Participants: 50 participants will be recruited to the trial.

Method: At baseline each participant will have a detailed interview with the study doctor to assess past medical history and previous symptoms attributed to statins and assess if they are eligible to be enrolled. Eligible participants will be enrolled on InForm which will allocate each participant a random predefined order to take the study interventions in. These random codes will be generated by the ICTU statistician and supplied to the production pharmacy. The participant will be dispensed HDPE containers which are in this pre-specified order assigned on inform. Each participant will receive 12 sets of HDPE containers pre-labelled. 4 sets of HDPE containers will contain no medication, 4 will contain 1-month supply of matched placebo and 4 will contain 1-month supply of atorvastatin 20mg. At the start of the next calendar month after the screening visit the participants will commence the trial intervention. The research nurse will call the participant to remind them to start on the 1st day of the next month after screening and thereafter the participants will also receive a monthly reminder on their phone to switch to the next set of HDPE containers each month. Each day participants will rate their daily symptom on a phone application and will also complete 3 additional questionnaires on a monthly basis. The study nurse will call the participant at the end of each month to assess their progress in the trial. Each participants will return their boxes at dispensing visits (if applicable) and at the study end in order for a pill count to be undertaken to assess medication adherence. The placebo and atorvastatin pills will be visually identical.

The study enrols participants not intending to re-start clinical use of statins. Participants' other medications will continue to be managed as normal by their own physicians, with no restriction on starting, stopping or changing doses For safety reasons the participant's own physician will be asked to consult the investigators prior to consideration of starting, or amending the dose of, any other lipid lowering medication

3.4 STUDY OUTCOME MEASURES

For the trial, each participant will receive a smartphone or if preferred can have the application downloaded to their existing phone to allow real-time daily documentation of symptoms experienced on a visual analogue scale of 0-100. Example screen-shots (which will be further refined based on the findings from the pilot study) are shown in Appendix 3. Participants will receive training on the simple touch-screen interface and a leaflet with further information will also be provided. There is an optional daily reminder that can be disabled if intrusive. Participants will rate symptoms every day, with the daily scores aggregated into a monthly score. This is preferable over scoring only once a month, because participants may struggle to remember and aggregate their symptom burden especially if it varies between days.

Each month participants will fill out two validated questionnaires on the impact of their side-effects on their quality of life. These are EuroQol (EQ-5D-3L),[34] a well-validated measure of health related quality of life, and the Treatment Satisfaction

Questionnaire for Medicine (TSQM) questionnaire, a validated treatment satisfaction questionnaire. EQ-5D-3L assesses five domains of health and overall self-rated health using a visual analogue scale. EQ-5D-3L is conventional for assessing efficacy of medication on quality of life but may not be sufficient for assessing side effects,[35] therefore the TSQM[36] questionnaire will also be used. Use of both a health related quality of life questionnaire and a treatment satisfaction questionnaire will allow assessment of participants' multiple health states, overall self-rated health status and treatment satisfaction, and provide a test of both convergent validity and measurement invariance for the monthly aggregate symptom burden score.

We will also ask participants to fill in a short questionnaire detailing any potentially confounding life events over the previous month e.g. change of daily routine, holidays, bereavement, etc. At the end of study visit, participants will have an exit interview exploring the nature of symptoms occurring during the study in case they may differ from those described in the baseline interview. Participants will also be shown their individual nocebo proportion at the end of study visit. The Participantis then able, as in normal life, to decide to continue on a statin or not. We will follow-up the participants at 6 months after the end of study visit and evaluate:

a) Whether they are now taking a statin and, if not, the reason
b) Whether they currently believe that most of the side-effects previously attributed to the statin, were indeed a pharmacological effect of the statin.

4 PARTICIPANT ENTRY

4.1 INCLUSION CRITERIA FOR MAIN TRIAL:

- Aged 18 years or older
- Previously taken one or more statins
- Withdrawn from statins because of perceived side effects
- Developed side effects within 2 weeks of initiation
- Clinical indication for statins for primary or secondary prevention of cardiovascular disease or dyslipidaemia, on either no medication or non-statin lipid lowering therapy (e.g, ezetimibe)

4.2 EXCLUSION CRITERIA FOR MAIN TRIAL:

- History of neuropathy
- Regularly taking prescribed analgesia
- History of a chronic pain condition
- History of severe mental illness (as their experience of symptoms may already be altered)
- Current use of fibrates (because of the risk of interaction with statins but will not exclude participants taking ezetimibe).
- Severe previous reaction or reaction considered immunological, such as anaphylaxis, facial swelling, severe rash, muscle ache *with* rise in serum

creatine kinase, inflammatory myopathy, rhabdomyolysis or liver function abnormalities (AST or ALT greater than 3 times upper limit or normal).
- Side-effects taking longer than 2 weeks to develop (because in such participants much longer blocks of treatment would be required, if the present study is positive such studies will be planned for the future)*.
- History of statin intolerance with drug interaction to antiretroviral drugs.
- History of statin intolerance to any other drug.
- Pregnant or breast feeding.
- Side effects taking longer than 2 weeks to present.
- In clinical judgement of study doctor, participant should not participate.

**All participants excluded for this reason will be logged so that the proportion excluded will be known. The study will be explained to consecutive eligible participants, and those giving informed consent will be recruited.*

4.3 WITHDRAWAL CRITERIA

If during the study, participants choose to re-start clinical statin therapy, they will withdraw from the study and start open medication.

4.4 UNBLINDING PROCEDURE

In the unlikely event unblinding is necessary it will be possible for the Chief Investigator to quickly and easily unblind to treatment using the unblinding function of the trial database. A back-up unblinding list will be held at the pharmacy.

5 PHARMACOVIGILANCE

5.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An *AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.*

Adverse Reaction (AR): all untoward and unintended responses to an IMP related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Unexpected Adverse Reaction: an AR, the nature or severity of which is not consistent with the applicable product information (summary of product characteristics). When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the summary of product characteristics

which occur in a more severe form than anticipated are also considered to be unexpected.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

- Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction related to an IMP that is both unexpected and serious.

5.2 CAUSALITY

Most adverse events and adverse drug reactions that occur in this study, whether they are serious or not, will be expected treatment-related toxicities due to the drugs used in this study. The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below.

If any doubt about the causality exists other clinicians may be asked to advise in some cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA will be informed of both points of view.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the

	influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

5.3 REPORTING PROCEDURES

There is only one study site and the principal investigator is also the chief investigator of the study. All adverse events will be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting will be directed to the Chief Investigator in the first instance. A flowchart is given below to aid in the reporting procedures.

5.3.1 NON SERIOUS ADVERSE REACTIONS/ADVERSE EVENTS

All such toxicities, whether expected or not, should be recorded in the toxicity section of the relevant case report form

5.3.2 SERIOUS ADVERSE REACTIONS/ADVERSE EVENTS

Fatal or life threatening SAEs and SUSARs should be reported on the day that the site is aware of the event. The SAE form asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality (i.e. unrelated, unlikely, possible, probably, definitely). The responsible investigator should sign the causality of the event. Additional information should be gained within 5 days if the reaction has not resolved at the time of reporting.

5.3.3 SERIOUS ADVERSE EVENTS

An SAE form should be completed by the site within 24 hours. However, hospitalisations for elective procedures of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the <name of REC> where in the opinion of the Chief Investigator, the event was:

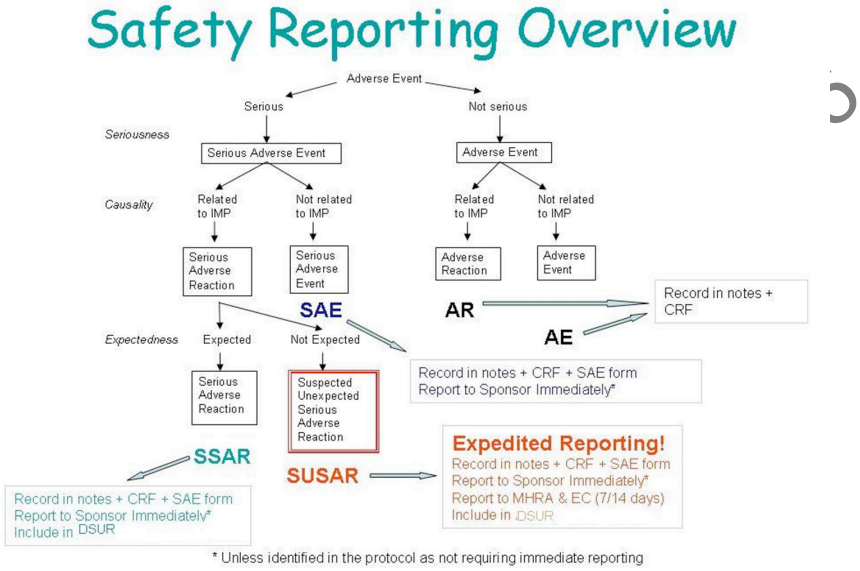
- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

5.3.4 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS

In the case of suspected unexpected serious adverse reactions, the staff at the site should:

Complete the SAE case report form and send it immediately (within 24 hours, preferably by fax), signed and dated to the MHRA, REC and sponsor

together with relevant treatment forms and anonymised copies of all relevant investigations. The study team will notify the MHRA, REC and sponsor of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All local investigators will be informed.



6 IMP MANAGEMENT AND ACCOUNTABILITY

6.1 MANAGEMENT/SUPPLY OF IMPS

An up-to-date summary of product characteristics (SmPC) of Atorvastatin will be included in the Trial Master File (TMF), which will be reviewed at least annually and any change should be notified and an updated SmPC added to the TMF.

Research staff will be delegated IMP management responsibilities by the CI. The CI in conjunction with research staff delegated IMP management responsibilities must:

a. Maintain records that document shipment, receipt handling, return and destructions of the IMP
b. Maintain a system for retrieving IMPs and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired reclaim).
c. Maintain a system for the handling of unused IMP(s) and for the documentation of returned IMPs
d. Maintain records of batch sample analyses, characteristics and storage conditions, e.g. temperature logs.

6.2 DRUG ACCOUNTABILITY

Drug accountability logs will be kept for dispensing IMP and for reconciling returned medication. The accountability log will detail:

- Subject identification code
- Date dispensed
- Dose
- Date of expiry
- Quantity dispensed
- Batch number
- Date returned
- Quantity returned
- Recorder's initials

All IMPs should be stored and dispensed by the delegated research staff and managed to the same standards as licensed medicines.

6.3 LABELLING

The IMP (atorvastatin 20mg OD or placebo) will be labelled, to ensure all supplies are in consistent packaging with consistent labelling to maintain blinding. They will be labelled with:

i. The name of the investigator
ii. Sponsor:
iii. Product name, form and strength or placebo
iv. Date of supply
v. Name and address of site
vi. Trial specific code
vii. Code for the trial subject
viii. Directions (as specified)
ix. "Keep out of reach of children"

As it is a blinded trial, the coding system for the investigational product includes a mechanism that permits rapid identification of the product in the unlikely case of a medical emergency.

6.4 TRIAL SPECIFIC SOPS

The CI, in conjunction with the research staff at the site should ensure that the following trial specific SOPs are in place before starting the trial:

- Receipt and recording of safe delivery of IMPs
- Safe Handling and storage of IMPs
- Code Breaking
- Preparation and dispensing of IMPs
- Return and disposal of unused IMPs
- Maintaining a pharmacy study file

7 ASSESSMENT AND FOLLOW-UP

Participants will attend a screening visit where the study doctor will receive written informed consent from them if they decide to participate. Then the study doctor will assess the participants eligibility for the study by evaluating their past medical history and previous statin intolerance. Participant's blood pressure will also be measured and if a participant does not have a recent lipid profile recorded in the last 12 months, they will be offered the option of having one undertaken as part of the screening visit. The study doctor will determine if the participant is suitable to be enrolled in the study. If suitable, they will be enrolled on inform.

Unscheduled assessments will not be performed unless participants develop adverse events which the chief investigator considers 'related' to the trial procedure or Atorvastatin therapy.

Scheduled follow-up telephone calls will be undertaken during every month during the 12-month period of the trial. Furthermore, participants scoring will be monitored by study nurse and if they show severe discomfort or if participants are not scoring on their phone unscheduled telephone follow-up calls will be made and if required a unscheduled study visit to see the study doctor and perform unscheduled tests as deemed necessary by the study doctor.

End of study will be defined as when the specified number of patients have been recruited, all patients have completed the 18-month phone interview and the database is locked.

The 12-month follow-up contact may be combined with the end of study visit, if so this would be a face-to-face visit at the study centre. The end of study visit may take place up to 31 days after the 12-month telephone follow-up.

8 STATISTICAL AND DATA ANALYSIS

The daily Quality of life scores will have their distribution described by the mean and standard deviation or, if not normally distributed, median and interquartile range. These scores will then be aggregated to month average scores. The r_{WG} and ICC statistics will be used to assess within-subject agreement and group mean reliability. To establish the measurement properties (i.e. convergent validity and measurement invariance) of the new measure we will examine the correlations between the month averages and each of the two monthly validated scoring systems (EQ-5D-3L and TQSM). A strong correlation ($r>0.4$) will reflect satisfactory convergent validity. The stability of the correlations across the 12 months will reflect the degree of measurement invariance. We will test this formally by a pair of path analysis models using M*plus*: one model in which the within-time correlations between the monthly aggregate of the new measure and the validated measure (i.e. EQ-5D-3L and TQSM) are fixed across time, and another where they are allowed to differ. If the latter model does not offer a significant improvement in model fit (assessed by chi-squared and fit indices) this suggests measurement invariance.
Our study's principal hypotheses will be tested as follows:

Hypothesis 1 will be tested by calculating the proportion of respondents completing the study, and the corresponding 95% confidence interval for this estimate, and examining whether the confidence interval lies completely above a value of 0.3 or not.

To test **Hypothesis 2**, comparisons between the average monthly wellness (measured by the monthly aggregate of our daily measurement tool) resulting from no treatment/placebo/statin treatment periods will be made using a longitudinal multilevel model. The most basic model to test hypothesis 2 would be:

SYMPTOMBURDEN = b0 + b1*TIME + b2*TREATDUM1 + b3*TREATDUM2

where TREATDUM1 is the contrast between placebo and no treatment, and TREATDUM2 is the contrast between statin and no treatment. We would test whether b3 > ½ b2, that is, the placebo increases symptoms by more than half as much as the statin, with no-treatment as a reference for both. However other potential confounders at the time (i.e. month) level and/or subject level (e.g. life events, gender, age) will be included in the model, and retained if they explain non-trivial variance.

A *p* value of < 0.05 will be considered statistically significant, and a two tailed test will be applied. Power calculations and considerations for hypothesis 1, 2 and 3 are shown below.

8.1 POWER CALCULATIONS

Hypothesis 1: We hypothesise that of the patients enrolling for the study, 50% or more will complete the study. Our intention is to report the proportion of patients completing the study and its 95% confidence interval. Based on the binomial principle, $SE_p = \sqrt{p \cdot q / n}$, the number of patients planned after the calculation below (50) will permit this proportion to be stated with a 95% confidence interval of $\pm 1.96\sqrt{\frac{1}{2}\cdot\frac{1}{2}/50}$. Thus the proportion will be reported with a margin of error of ±14% or smaller. If the long-run proportion of patients who would finish the study is ~70%, then a sample size of 50 gives 85% power to detect this at the 5% significance level.

Hypothesis 2: More than half of side effects of statins are non-pharmacological. Each "nocebo proportion" will be a value which, for the sake of this calculation, we will assume to be between 0 and 1. We aim to report an average nocebo proportion for the population that has a 95% confidence interval of ±10%. To achieve this, assuming a worst-case scenario of individual-patient values scattered uniformly from 0 to 1 (i.e. SD = 1/√12 = 0.29) we require the number of patients studied to be ≥*n* where 0.29/√*n* ≤0.10/1.96, i.e. *n*>(1.96×0.29/0.10)^2=36. We plan to recruit **50** participants.

In reality, the calculated nocebo proportion will likely be a fairly large fraction of 1 and occasionally greater than 1; it is unlikely to be less than 0; therefore these calculations are conservative.

Hypothesis 3: Individual patients can receive a precise evaluation of their nocebo fraction. We plan to present each patient with their own nocebo fraction with a 95% confidence interval, so that they can know the margin of error and cannot attribute it to fluke. The statistical properties of ratios of measurements are nonlinear, so necessarily we are applying some simplifications in these power calculations. First,

we shall assume that the active tablet arm has substantial side effects. Individual patients will represent this severity with different absolute numerical magnitudes, so for this power calculation we shall define:

A_1, A_2, A_3 … A_{112} as the 4×28 daily severity scores on active treatment

N_1 … N_{112} as the 4×28 daily severity scores on nocebo

Z_1 … Z_{112} as the 4×28 daily severity scores on no medication (zero tablets)

Let the averages of these respective data be m_A, m_N and m_Z, and their standard deviations s_A, s_N, s_Z.

We wish to express $(m_N-m_Z)/(m_A-m_Z)$ i.e. the nocebo fraction, and its standard error. As long as m_Z is small compared to m_A and m_N, and s_A is not large in relation to m_A, a reasonable approximation to the fractional standard error of the nocebo fraction $(m_N-m_Z)/(m_A-m_Z)$ is $(s_A/m_A + s_N/m_N)/\sqrt{112}$. Real-life months are mostly slightly longer than 28 days, so the actual standard error will be very slightly smaller. We expect symptoms to be relatively high on tablets (whichever type), i.e. the A and N values will not be scattered over the full spectrum but clustered at the upper range for that patient. Thus sA/mA and sN/mN will each be of the order of ~0.2. The standard error of the nocebo fraction would therefore be 0.037, i.e. the nocebo fraction, a percentage, could be given with a 95% margin of error of ±7 percentage points.

9 MONITORING

9.1 RISK ASSESSMENT

This study is adopted by the Imperial Clinical Trials Unit (ICTU). ICTU will risk assess the study and undertake monitoring responsibilities relevant to the trial's estimated level of risk.

10 REGULATORY APPROVALS

10.1 CLINICAL TRIALS AUTHORISATION

The study will be performed in compliance with UK clinical trial regulations. Clinical Trial Authorisation from the Medicines and Healthcare products Regulatory Authority (MHRA) will be obtained prior to the start of the study. In addition, the Regulatory Authority must approve amendments (as instructed by the Sponsor), receive SUSAR reports and annual safety updates, and be notified of the end of the trial.

10.2 ETHICAL APPROVAL

Prior to enrolment of subjects, written approval from the REC must be obtained for named sites, the protocol and any amendments, the Patient Information Sheet and Consent Form, any other written information that will be provided to the subjects, any advertisements that will be used and details of any subject compensation. The study must be submitted for Site Specific Assessment (SSA) at Imperial College Healthcare NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the World Medical Assembly, 7th Version of the Declaration of Helsinki (2013). The REC will be sent annual progress reports,

annual safety reports and will also be informed about the end of the trial within the required timelines.

10.3 INFORMED CONSENT

Prior to informed consent being received participants will be given ethically and trust approved version controlled information sheets regards the study and given at least 24 hours but preferably at least a week to read this information prior to consent.

For the pilot study the research nurse who is experienced in receiving informed consent for qualitative research will undertake the informed consent process with participants.

For the main trial participants will be consented by the Research Fellow or Chief investigator/Principal investigator. The research fellow will be a cardiology SpR (MB BS MRCP); who will be able to assess mental capacity and understands the principles of informed consent.

Only participants who are able to fully consent to the study will be recruited. As there is an extra time commitment associated with the study, and much of the study is in addition to usual care, only participants who have capacity to refuse will be approached. There is no funding available for translation so people who cannot speak or write in English will be unable to participate. It will be highlighted to participants that they can withdraw their consent at any stage.

10.4 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

10.5 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

10.6 SPONSOR

Imperial College London will act as the Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

10.7 FUNDING

The British Heart Foundation are funding this study. Travel reimbursement for site visits has been allocated.

10.8 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

11 TRIAL MANAGEMENT

11.1 TRIAL MANAGEMENT GROUP

A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the progress of the trial and will include independent members.

The day-to-day management of the study will be co-ordinated through Imperial College London by research nurse Ms Frances Wood, who will be supervised by research fellow Dr Judy Finegold and Consultant Cardiologist Professor Darrel Francis.

The study has been adopted under the Imperial Clinical Trials Unit (UKCRC ID number 18).

11.2 DATA MONITORING COMMITTEE

A Data Monitoring Committee (DMC) will be convened to review safety data annually and advise the TMG if the trial should continue. A Charter will be devised to list the roles and responsibilities of the members.

12 DATA MANAGEMENT

Inform will be used to manage the data for the study. InForm is a validated data capturing system with a full audit trail.

13 ARCHIVING

Following the end of the study, when deemed practical, all essential documents will be archived for a minimum of 10 years as per Imperial College London guidelines.

14 PUBLICATION POLICY

We plan to disseminate the results of this study through publication in peer reviewed scientific journals, conference presentations and publication on Imperial College London website.

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SIGNATURE PAGE 1 (Principle Investigator)

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title:

Sponsor's reference :

Signed: _____

Professor Darrel Francis
Consultant Cardiologist
Imperial College London

Date: _____

SAMSON Protocol No: 1.0 Version 1.0 6th September 2015

SIGNATURE PAGE 2 (SPONSOR)

The signatures below constitute approval of this protocol by the signatory.

Study Title: 15SM2947

Sponsor's reference :

Signed: _____

Ruth Nicholson
Research Governance Manager
Joint Research Compliance Office
Imperial College London and Imperial College Healthcare NHS Trust

Date: 22/03/16

Confidential Page 22 of 67

Appendix 3: Information sheet and consent form for the SAMSON trial

Peart-Rose Research Unit, Imperial College London,
1st Floor, Block C,
Hammersmith Hospital, Du Cane Road,London, W12 0HS

P: 0207 594 9647
F:0203 3137348
E: frances.wood1@nhs.net

Dear Sir/ Madam,

Participant Information Leaflet

Clinical Trial:
Self Assessment Method for Statin side-effects Or Nocebo (SAMSON)

We invite you to take part in a research study. Before you decide, it is important for you to understand why the research is being carried out and what it will involve. Please take time to read the following information and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

PART 1
Background

High blood levels of cholesterol cause cardiovascular disease (heart attacks and strokes). Statins lower cholesterol and are widely used to prevent cardiovascular disease. Despite their beneficial effects, some people develop side effects which may lead them to the stop taking their statin medication.

Why have I been approached?

You are being invited to take part as we think you have previously experienced side-effects whilst taking a statin.

What is the purpose of the study?

It is unclear if all the side effects experienced whilst taking statins are specifically caused by the medication. Symptoms may simply arise by chance or coincidence. This research will allow participants to assess for themselves what proportion of the symptoms they experience can be correctly attributed to statins.

Why are we interested in statin side-effects?

We know that side effects may significantly impact a person's quality of life. In clinical trials, participants experience side-effects whilst they are taking both active medication (e.g. statins), and whilst taking placebo pills (dummy tablets). This does not imply that side-effects are 'imagined' when taking the placebo, but rather that the experience of

side-effects is complicated. Some people may subconsciously feel negatively about taking daily medication. For example they may be concerned about the risk of side effects and therefore get negative reactions even to dummy tablets; this is termed the Nocebo effect or “Negative Placebo” effect. It may be difficult to determine if side effects are truly caused by the active medication.

Why should I take part in this study?
Your involvement will help to answer important questions about side effects that cause people to stop taking statins. This is a big problem as many people find it difficult to tolerate preventive medication. Understanding this difficulty may improve patient care in the future.

We will interpret your study data to see what proportion of the side effects you attribute to statins is directly due to the medication. You will then be able to discuss future treatment options with the study doctor.

What would this study involve?
The study will last one year. You will only need to visit the research clinic two or three times. We will then talk to you on the phone six months after the study has finished.

Visit 1: First visit (baseline)
Before your first visit, we will request information about your medical history from your GP. Details will include your past statin use and previous cholesterol results. We will ensure it is safe for you to participate and to restart statins. You will visit us at the research clinic at the Hammersmith Hospital on a convenient day. The doctor will answer your questions and if you still want to participate, we will ask you to sign a consent form which indicates your agreement to take part in the study. We will measure your blood pressure and do a cholesterol blood test if you have not had this done within the last 12 months.

If you are eligible and decide to participate you will be given a case containing 12 individual boxes labelled 1 to 12. There will be 4 boxes containing no medication, 4 boxes each containing a 1-month supply of placebo (dummy) tablets and 4 boxes containing a 1-month supply of atorvastatin 20mg. You will not be able to tell the difference between the placebo and the atorvastatin tablets. During the study you will be asked to change your medication on a monthly basis.

The contents of the boxes (nothing, placebo or atorvastatin 20mg) will be arranged in a random order, that neither yourself nor the study team will know.
Therefore, each day for one month you will receive either:

1) No treatment, or
2) A Placebo (dummy) pill on a daily basis, or
3) Atorvastatin 20mg on a daily basis

The atorvastatin and placebo pills will look identical; therefore you will not know which you are taking. You will be on either atorvastatin, placebo or no treatment each for a total of four months. If, for some reason, we need to distinguish the placebo and the atorvastatin we can reveal this by breaking a code.

You will record the symptoms you experience every day during the study. This will be done with a simple application on a smartphone. It takes less than one minute per day to record symptoms. The study nurse will provide you with a mobile phone or if preferred the application can be downloaded to your own phone. If you do not have wifi at home, we will give you a phone that has credit to enable internet connection. The study nurse

will teach you how to use the application. We will also give you a leaflet with further instructions and a questionnaire booklet. A reminder can be setup on the phone to prompt your recording symptoms.

At the end of each month we will ask you to complete brief questionnaires assessing your quality of life and important recent events (e.g. change of daily routine, holidays, bereavement, etc). The study nurse will ring you at the end of each month to check how you are and to remind you to complete the questionnaires.

Throughout the study it is important that you only take medication when you wish to. If you feel unwell and wish to stop the study tablet, then you will record this as the maximum score for side-effects. You will stop study medication for the rest of that month and re-start with the next box the following month (if you are happy to continue).

Visit 2: Resupply of medications

You may need to attend a brief visit to return used medications and collect a new supply of medication from the study centre; this will take place approximately midway through the trial. The study nurse will inform you at your baseline visit if this is necessary.

Monthly phone calls

The study nurse will telephone you each month to check on your progress.

Visit 3: end of study visit

At the end of the study we will work out your daily side-effect scores over the year. We will calculate the proportion of your symptoms directly attributable to the statin. You can discuss these results with the study doctor and decide whether they influence you choice about continuing with statins after the study. We will write to your GP with the results, and based on our discussion with you, we will make recommendations about your future medication.

Telephone call at six-months after study end

Six months after the study has finished, we will arrange a final telephone call with you. The aim of this telephone call is to understand whether being informed of the results of the study has changed your opinion on future treatment options. It will also help us to better understand your experience of trial participation.

You will not be able to take part in this Study if:

- Your doctor thinks that statins previously may have caused you a severe reaction.
- Your doctor thinks that you may have previously suffered an allergic reaction to statins e.g. facial swelling, severe rash or muscle ache with rise in muscle enzymes.
- You are pregnant, breast feeding or are likely to become pregnant during the Study.
- Your doctor thinks that you are suffering from any condition that may prevent you from completing the Study
- You suffer from neuropathy or regularly take prescribed pain killers e.g. for a chronic pain condition.
- You are taking a lipid-lowering medication called a fibrate.
- Your side-effects generally took longer than 2 weeks to develop.

Do I have to take part?

Your participation is voluntary. If you decide not to take part, this will not affect your normal standard of care. If you do take part, you are free to withdraw at any time without giving a reason.

What about other medications I am taking?
Your routine medications will continue to be managed by your usual doctor. There will be no restriction on starting, stopping or changing doses of other existing medication or new medications. It is expected that you will not restart routine statin medication during the year of the study. However, if you should wish to do so, you may withdraw from the study at any time and restart routine statin medication.

What happens if I have a side effect?
If you experience side effects, you should contact the study nurse. You may be asked to attend the research centre for further assessment.

Cost and reimbursement?
All travel expenses related to the study will be reimbursed. We need to collect receipts.

Are there any risks or discomforts?
There is a risk of experiencing side-effects by taking statins again. You will have instructions on what to do if you experience side effects.

What if something goes wrong?
We do not anticipate that you will come to any harm during this study and we will ensure you will receive high quality care throughout. However, if through our negligence, you should suffer any harm then you will be compensated and a full investigation will be conducted. Imperial College London holds insurance policies that apply to this study. If you experience serious and enduring harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (contact details given below). The normal National Health Service complaint complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial College Clinical Research Office.

Will my taking part in this study be kept confidential?
If you agree to take part in this study, you will be given a unique study ID number. All information that is collected about you will be held on a password-protected computer. All paper copies of study data will be stored under ID number and kept in locked offices within the research facilities. Access to data will be available to the research team, the sponsor and possibly by UK regulatory authorities of clinical studies. Any information you provide will be held in the strictest confidence; however, we have a duty of care to notify you if any of the findings are clinically important.
If you agree, we would contact your GP to inform them you are participating and will provide them with information regarding the study.

Contact details for further information
Now or during the course of the study, if you have any questions concerning this study or your rights as a participant, you should contact your study doctor Prof Darrel Francis, or

nurse Frances Wood on 0207 594 9647.Or for independent advice, please contact the NHS patient advisory liaison service (PALS) 020 3313 0088.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2.

PART 2

What if relevant new information becomes available?

Sometimes during the course of a research project, new information becomes available about the issues being studied which could influence participants' willingness to participate. Although unlikely in this study, if this happens, your research doctor will tell you.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions (Contact numbers above). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Department Telephone: 020 3313 0088 or email: pals@imperial.nhs.uk.

Will my taking part in this study be kept confidential?

All information, which is collected about you during the course of the research, will be kept strictly confidential. Access to data will only be available to the research team, the sponsor and the UK regulatory authorities of trials. Data collected will be kept on secure computers in the hospital. Also these data will be coded and therefore anonymous. The data will eventually be used for the scientific reporting of this research. The handling, processing, storage and destruction of your data will be compliant with the Data Protection Act 1998. With your consent we will notify your GP about your enrolment in this study.

What will happen to the results of the research study?

Scientific data from this study may be presented at meetings and published so that the information can be used to help others, but your participation in the study will not be made known and will be kept strictly confidential. If you take part in the study we will send you a summary of the findings from this research, and its implications.

Who is organising and funding the research?

This research has been organised by Imperial College London. It is funded by the British Heart Foundation.

Who has reviewed the study?

This project has been reviewed by London Brent ethics committee, REC reference: 15/LO/1761.

Thank you for taking the time to consider participating in this study.
If you wish to participate a copy of this information sheet and of the consent form will be given to you.

Imperial College London

Imperial College Healthcare NHS Trust

SAMSON
Self-Assessment Method for Statin side effects Or Nocebo

British Heart Foundation

CONSENT FORM

Clinical Trial
Self Assessment Method for Statin side-effects Or Nocebo (SAMSON)

Chief and Principal Investigator: Professor Darrel Francis
Imperial College London, Peart-Rose Research Unit, 1st Floor, Block C, Hammersmith Hospital, Du Cane Road, London, W12 0HS

Please read each statement	*Please initial as applicable*
I have read the Patient Information Sheet Version 1.1 (Dated: 11/12/2015).	Yes …… No……
I have received enough information about this study, had the opportunity to ask questions and I am satisfied with the answers to my questions.	Yes …… No……
I have spoken to Dr.....……	
I understand that I am free to withdraw from the study at any time without giving a reason and without affecting my future care or legal rights.	Yes …… No……
I understand that if I withdraw from the study early, the data collected whilst I was on the study will be retained and used by Imperial College London for the purposes described in the participant information sheet.	Yes …… No……
I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from Imperial College, from regulatory authorities or from Imperial Healthcare NHS Trust. I give permission for these individuals to access my records.	Yes …… No……
I agree for my contact details to be kept on record for future research studies at Imperial College London	Yes …… No……
I understand that a product(s) may be developed through the use of my medical information collected during this study but neither Imperial College London nor the researchers will compensate me if this happens and I do not have any rights to future inventions. I give my permission for the processing of my information.	Yes …… No……
I agree to have a lipid profile (blood test) done for the study.	Yes …… No……
I agree to my GP being informed about my participation in this research study.	Yes …… No……
I agree to take part in this research study.	Yes …… No……

Appendix 4: SAMSON trial letter and source data request to GPs

Imperial College London,
Peart-Rose Research Unit,
1st Floor, Block C,
Hammersmith Hospital,
Du Cane Road,
London
W12 0HS

P: 0207 594 9647
F:0203 3137348
E: frances.wood@imperial.nhs.uk

[Insert date]

Doctor,

Dear Sir/Madam
Re:
Address:
Study title: Self-Assessment Method for Statin side-effects Or Nocebo (SAMSON) Trial

Your patient has expressed an interest in participating in the "Self Assessment Method for Statin side-effects Or Nocebo (SAMSON)" trial. Your patient has subsequently been booked to come in for a screening visit and, if eligible, he/she will be offered to be enrolled in the trial.

The study is based at Hammersmith Hospital, and is funded by the British Heart Foundation.

The primary hypothesis is to assess, for each individual patient, to what extent experienced symptoms are associated directly with the pharmacological action of the statin.

If you have no objection to your patient's participation, please complete the attached form to confirm their details and relevant medical history and fax it back to us as soon as possible.

Please contact us if you have any concerns about your patient's participation or any questions.

For your information, a copy of the General Practitioner information sheet is enclosed, giving more details about the study,

Thank you for your time and your help is greatly appreciated.

Yours sincerely
Professor Darrel Francis
Imperial College London
Encs: Patient details confirmation form & GP information Sheet

GP Name: ,

GP Address:

I confirm that: **Name:**
Address:
DOB:

Is currently registered at our practice

Year of first diagnosis of dyslipidaemia if known?	
Most recent lipid profile	Date:
Total Cholesterol	
HDL cholesterol	
LDL cholesterol	
HDL:TG ratio	
Please list all current lipid lowering medication (name and dose):	
Details of any previous intolerances to lipid-lowering therapy (including name of therapy, dose prescribed)	
If previous intolerance to lipid-lowering therapy please describe the nature of the intolerance. *e.g. In particular was there any evidence of anaphylaxis or severe allergy. If the symptoms were muscle related was there any evidence of elevation in creatinine kinase elevation or inflammatory myopathy? Please include all relevant information and details and any relevant investigations performed at that time due to the intolerance e.g. blood tests*	
Most recent BP (mmHg)	
Are they prescribed anti-hypertensives?	YES/NO
Smoking status	Never smoked Ex-smoker Current smoker
Diabetes: If yes please specify whether Type I or II	YES/NO, if yes please specify type 1 or 2.
History of Myocardial infarct, stroke, peripheral vascular disease or reno-vascular disease	YES/NO, if yes please describe

GP Signature: **…….....**

GP Print Name: **…….....…….Date:** **__ __ / __ __ / __ __**

*** Please return by fax to 0203 313 7348***

Appendix 5: Example of case report form for SAMSON screening visit ;

Patient Initials Patient Trial Number Date

SAMSON

Screening

- ☐ Participant Initials ___
- ☐ Date of Birth __/__/____
- ☐ Informed Consent
  - ○ Date signed __/__/____
  - ○ Version _._ Date of version __/__/____
- ☐ Date of Screening __/__/____
- ☐ Gender
  - ○ Male ○ Female
- ☐ Height ___cm
- ☐ Weight ___._kg
- ☐ Ethnicity
  - ○ White
    - ○ White British
    - ○ White Irish
    - ○ Other White
      Please specify_____
  - ○ Mixed
    - ○ Mixed White and Black Caribbean
    - ○ Mixed White and Black African
    - ○ Mixed White and & Asian
    - ○ Other Mixed
      Please specify_____
  - ○ Asian
    - ○ Indian
    - ○ Pakistani
    - ○ Bangladeshi
    - ○ Chinese
    - ○ Other Asian
      Please specify_____
  - ○ Black
    - ○ Black Carribean
    - ○ Black African
    - ○ Other Black
      Please specify_____
  - ○ Any other Ethnic Group_____
  - ○ Not reported
- ☐ Highest completed qualification?
  - ○ Primary School
  - ○ Secondary School
  - ○ Undergraduate degree
  - ○ Postgraduate degree or diploma
  - ○ Technical/vocational qualification
- ☐ Allergies

  - ○ No Known Allergies

Patient Initials | Patient Trial Number | Date

- Yes Known Allergies
  Please specify_____

Inclusion

- Aged 18 years or older — Yes
- Previously taken one or more statin — Yes
- Withdrawn from statins because of perceived side effects — Yes
- Developed side effects within 2 weeks of initiation of statin — Yes
- Clinical indication for statins for primary prevention or secondary prev of cardiovascular disease or dyslipidaemia — Yes

Exclusion

- History of any condition that causes chronic pain — Yes
- History of severe mental illness — Yes
- History of statin intolerance with creatine kinase elevation greater thar times the upper limit of normal — Yes
- History of statin intolerance with inflammatory myopathy — Yes
- History of statin intolerance with anaphylaxis — Yes
- History of statin intolerance with myalgia and rise in serum creatine kir — Yes
- History of statin intolerance with rhabdomyolysis — Yes
- History of statin intolerance with liver function abnormalities, defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times the ULN — Yes
- Currently taking fibrates — Yes
- Currently taking antiretrovirals with known drug interact to statins — Yes
- Currently taking any drugs other than antiretrovirals with known inter to statins — Yes
- Pregnant or breast feeding — Yes
- Side effects taking longer than 2 weeks to present — Yes
- In clinical judgement of study doctor, participants should not be enrol on the study — Yes

Pulse	___bpm
Blood Pressure 2	___/___ mmHg
Blood Pressure 3	___/___ mmHg

Is the participant taking any medication? — Yes

Generic Name	Total daily dose(units)	Start date	Continuing or End Date

Patient Initials | Patient Trial Number | Date

O ________________	_____	__/__/____	Yes or __/__/____
O ________________	_____	__/__/____	Yes or __/__/____
O ________________	_____	__/__/____	Yes or __/__/____
O ________________	_____	__/__/____	Yes or __/__/____
O ________________	_____	__/__/____	Yes or __/__/____
O ________________	_____	__/__/____	Yes or __/__/____
O ________________	_____	__/__/____	Yes or __/__/____
O ________________	_____	__/__/____	Yes or __/__/____
O ________________	_____	__/__/____	Yes or __/__/____
O ________________	_____	__/__/____	Yes or __/__/____
O ________________	_____	__/__/____	Yes or __/__/____
O ________________	_____	__/__/____	Yes or __/__/____
O ________________	_____	__/__/____	Yes or __/__/____
O ________________	_____	__/__/____	Yes or __/__/____
O ________________	_____	__/__/____	Yes or __/__/____
O ________________	_____	__/__/____	Yes or __/__/____
O ________________	_____	__/__/____	Yes or __/__/____
O ________________	_____	__/__/____	Yes or __/__/____
O ________________	_____	__/__/____	Yes or __/__/____
O ________________	_____	__/__/____	Yes or __/__/____
O ________________	_____	__/__/____	Yes or __/__/____
O ________________	_____	__/__/____	Yes or __/__/____

☐ Smoking status of participant

- O Never
- O Current smoker
  Please specify number of years smoking____
  Cigarettes per day____
- O Ex smoker
  Date started __/__/____
  Date stopped __/__/____
  Cigarettes per day____
- O Comments ___________________________________

☐ Has a blood sample been taken by the study team or has results of a previous test in last 12 months been transcribed?

O Yes O

If Yes, date sample taken __/__/____

O Total Cholestrol	__.__mmol/L
O HDL	__.__mmol/L
O LDL	__.__mmol/L
O Triglycerides	__.__mmol/L

☐ Has the participant experienced past and/or concomitant disease

Page 4 of 5

Medical condition or event	Start date	Ongoing or end date
O ________________	__/__/____	Yes or __/__/____
O ________________	__/__/____	Yes or __/__/____
O ________________	__/__/____	Yes or __/__/____
O ________________	__/__/____	Yes or __/__/____

Patient Initials	Patient Trial Number	Date
☐ _____	__/__/____	Yes or __/__/____
☐ _____	__/__/____	Yes or __/__/____
☐ _____	__/__/____	Yes or __/__/____
☐ _____	__/__/____	Yes or __/__/____
☐ _____	__/__/____	Yes or __/__/____
☐ _____	__/__/____	Yes or __/__/____
☐ _____	__/__/____	Yes or __/__/____
☐ _____	__/__/____	Yes or __/__/____
☐ _____	__/__/____	Yes or __/__/____
☐ _____	__/__/____	Yes or __/__/____
☐ _____	__/__/____	Yes or __/__/____
☐ _____	__/__/____	Yes or __/__/____
☐ _____	__/__/____	Yes or __/__/____
☐ _____	__/__/____	Yes or __/__/____

☐ Medical History Risk

- ☐ Angina or heart attack in 1st degree relative <60 — ☐ Yes ☐
- ☐ Chronic kidney disease — ☐ Yes ☐
- ☐ Atrial Fibrillation — ☐ Yes ☐
- ☐ On blood pressure treatment — ☐ Yes ☐
- ☐ Rheumatoid Arthritis — ☐ Yes ☐
- ☐ Diabetes — ☐ None — ☐ Type 1 ☐
- ☐ Indication for prescription of statins
  - ☐ Primary prevention of CVD — ☐ Secondary Prevention c
  - ☐ Other please specifiy_____
- ☐ Q-Risk Score _____

☐ Statin History

	Start Date	End Date	Dose (mg)	Frequency	Reason for stopping
☐ Atorvastatin	__/__/____	__/__/____	____	____	_____
☐ Simvastatin	__/__/____	__/__/____	____	____	_____
☐ Rosuvastatin	__/__/____	__/__/____	____	____	_____
☐ Pravastatin	__/__/____	__/__/____	____	____	_____
☐ Other Statin Name					_____
_____	__/__/____	__/__/____	____	____	_____

☐ Is the participant eligible for the trial? — ☐ Yes — ☐ No

If no, please specify

☐ Inclusion criteria violated

Patient Initials | Patient Trial Number | Date

○ Exclusion criteria violated

☐ Research Notes

Signature _____ Date _____

Appendix 6: Extract from Imperial Clinical Trials Unit Monitoring plan for SAMSON

Routine Monitoring Visit:

During the monitoring visit, the Study Monitor will perform Source Data Verification (SDV), as per the requirements detailed in Section 5. The monitor will perform the following activities during each site monitoring visit:

Activity	**Comments**
Review Patient Informed consent forms (original version and any amendments as applicable)	100% review of consent forms
Complete Source Data Verification (SDV) as per requirements of the risk assessment. Review lab reports to ensure Investigator (or designee) review and sign off on all lab reports	20% of randomly selected participants based on recruitment target 50
Review data quality - Assist site to resolve data queries - Ensure missing data is entered as soon as possible	
Review the Trial Master File • Review essential documents (e.g., CVs of new staff, updated insurance certificates/IB etc) • Ensure the SAE log is completed and filed in the TMF. • Ensure that all ethics reporting requirements have been met (e.g., Reporting of SAEs to ethics as per ethics approval) • Review Delegation of Duties and Site Signature Log • Ensure trial logs have been updated - Screening Log - Patient Identification Log - Sign the Monitoring Visit Log	Trial Management Group agreed that during COVID-19 pandemic the Monitor will perform remote review of e-TMF. Study documents will be scanned and uploaded to e-TMF by Study Coordinator.
Discussion with site staff including Principal Investigator on: - new issues and unresolved issues from monitoring visit - patient recruitment	

- reminder on SAE reporting requirements and to check status of SAE (resolved, ongoing, stop date etc) - site's compliance to protocol - timing of next visit	

Appendix 7: Statistical Analysis Plan for SAMSON

Imperial College London

Self-Assessment Method for Statin side effects Or Nocebo trial (SAMSON)

Statistical Analysis Plan
Version 1.0

January 14, 2020

Prepared by:
Statistics Collaborative, Inc.

CONFIDENTIAL

Imperial College London

SAMSON
Statistical Analysis Plan

January 14, 2020

Prepared by: Statistics Collaborative, Inc.

Author: _____ Date: 14-Jan-2020
Katrina Eprere, MPH
Biostatistician II

_____ Date: 14-Jan-2020
Janet Wittes, PhD
President

Approved by: Imperial College London

_____ Date: 24 Jan 2020
Darrel Francis, M.D.

CONFIDENTIAL

Contents

Exhibit

Abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Chemical
CI	confidence interval
CRF	case report form
EQ-5D-3L	EuroQol
ICH GCP	International Conference on Harmonisation Good Clinical Practice
ICTU	Imperial Clinical Trials Unit
MedDRA	Medical Dictionary for Regulatory Activities
PT	preferred term
SAMSON	self-assessment method for statin side effects or nocebo trial
SAP	Statistical analysis plan
SCI	Statistics Collaborative, Inc.
SD	standard deviation
SOC	system organ class
TSQM	Treatment Satisfaction Questionnaire for Medicine
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1. Introduction

This statistical analysis plan (SAP), which is based on protocol Version 1.2 dated August 1, 2019, defines the methods and analyses that Imperial College London plans to use to analyze the data from the Self-Assessment Method for Statin side effects Or Nocebo trial (henceforth, SAMSON). This study adheres to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928), and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It is being conducted in compliance with the protocol, the Data Protection Act, and other regulatory requirements as appropriate. If the protocol is subsequently amended, this SAP may be amended as well. Should the SAP and the protocol be inconsistent with respect to the planned analyses, the language of the SAP is governing.

2. Investigational plan

2.1. Study design

SAMSON is a randomized controlled trial evaluating in a cohort of participants the proportion of adverse symptoms truly due to the effect of statin rather than nocebo. The investigators plan to randomize participants to receive, in a random predefined order, the study interventions. Each participant will receive 12 sets of pre-labelled HDPE containers. Four sets of containers will contain no medication; four will contain a one-month supply of matched placebo; and four will contain a one-month supply of atorvastatin 20mg. At the start of the next calendar month after the screening visit, the participants will commence the trial intervention. The research nurse will call participants to remind them to start on the first day of the next month after screening; thereafter, the participants will receive a monthly reminder to switch to the next set of HDPE containers. Each day participants will rate their daily symptom on a phone application; they will complete three additional questionnaires each month.

2.2. Study objectives and outcome measures

Front-line clinicians cannot currently test whether symptoms an individual participant experiences are the pharmacological result of a statin or due to other phenomena (e.g., nocebo). The value of such a tool would be two fold:

- The tool would allow individual participants to establish for themselves whether they truly suffered a side effect from the drug or are victims of nocebo – which may in fact be more common.
- By separating the components, the tool would permit clinical researchers to explore the determinants of each, opening opportunities to obtain better clinical outcomes.

The main objectives of this study are to the following:

- To develop a method for determining for an individual participant what extent experienced symptoms are associated with the statin or merely reflect a nocebo effect.
- In a cohort of participants who have stopped statins because of adverse symptoms, to evaluate in what proportion the symptoms are truly due to the statin.

2.3. Study hypotheses

The study aims to test the following hypotheses:

- Hypothesis 1: More than 30% of participants enrolling into the study will complete it.
- **Hypothesis 2:** Overall, more than 50% of symptom burden is nocebo rather than pharmacological.

  The effect of nocebo effect on side effects will be defined as:

$$Nocebo\ effect = \frac{Nocebo\ component}{Total\ side\ effect\ (Pharmacological+Psychological)} = \frac{(average\ symptoms\ score\ on\ placebo - average\ symptom\ score\ on\ no\ medication)}{(average\ symptom\ score\ on\ statin - average\ symptom\ score\ on\ no\ medication)}$$

- **Hypothesis 3:** At six months after completion of the study, at least 50% of participants will either be taking statins or have declined statins for reasons other than perceived side effects.

2.4. Randomization

Eligible participants are enrolled on InForm, which allocates each participant a random predefined order during which to take the study interventions. The Imperial Clinical Trials Unit (ICTU) generates these random codes and supplies them to the production pharmacy.

3. Study schedule

3.1. Study days

Potential participants attend a screening visit during which the study doctor receives written informed consent from those who decide to participate. The study doctor then assesses the participants' eligibility for the study by evaluating their past medical history and previous statin intolerance. Participants' blood pressure is measured. Participants who do not have a recent lipid profile recorded in the last 6-months are offered the option of having one undertaken as part of the screening visit. The study doctor determines if the participant is suitable to be enrolled in the study. Suitable participants are enrolled on InForm.

Scheduled follow-up telephone calls are undertaken each month during the 12-month period of the trial. The study nurse monitors the participants' scores. If the scores show severe discomfort or if participants are not scoring on their phone, the study nurse makes unscheduled telephone follow-up calls and, if required, arranges an unscheduled study visit to see the study doctor who performs unscheduled tests deemed necessary.

The end of study will be defined to occur when the specified number of participants have been recruited, all participants have completed the 18-month phone interview, and the database is locked.

The 12-month follow-up contact may be combined with the end of study visit; if so this would be a face-to-face visit at the study center. If so, the month 12 visit must be completed before the scheduled unblinding. The end of study visit may take place up to 31 days after the 12-month telephone follow-up. The Exhibit presents the study visit schedule

Exhibit. Visit schedule

	D1	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M18
	Screening and Enrolment	Telephone follow-up	Telephone follow-up	Telephone follow-up	Telephone follow-up	Telephone follow-up	Telephone follow-up	Telephone follow-up	Telephone follow-up	Telephone follow-up	Telephone follow-up	Telephone follow-up	End of Study Visit	6 month Follow-up visit
Informed consent	X													
Inclusion/exclusion	X													
Demography	X													
Medical history	X													
Blood pressure	X													
Lipid profile (optional)	X													
Interview	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EuroQol	X	X	X	X	X	X	X	X	X	X	X	X	X	
TSQM	X	X	X	X	X	X	X	X	X	X	X	X	X	
Confounding life events questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	

3.2. Unscheduled visits

Unscheduled assessments are not performed unless participants develop adverse events that the chief investigator considers 'related' to the trial procedure or to atorvastatin therapy.

4. Sample size determination and power calculation

4.1. Sample size calculation – Hypothesis 2

Each "effect of nocebo" will be a value which, for the sake of the calculation in the protocol, was assumed to be between 0 and 1. The study aims to report an average effect of nocebo for

the population that has a 95% CI of ±10%. To achieve this, assuming a conservative scenario of individual-participant values scattered uniformly from 0 to 1 (i.e., SD = $1/\sqrt{12} = 0.29$), the number of participants to be studied will need to be $\geq N$ where $0.29/\sqrt{N} \leq 0.10/1.96$(i.e., $N > (1.96 \times 0.29/0.10)^2 = 36$. The investigators planned to recruit 50 participants. In all a total of 62 participants were screened and 60 were randomized.

5. Statistical analysis: general considerations and conventions

Descriptive and inferential statistics will be used to summarize results of the SAMSON study. Continuous variables will be summarized using the number of subjects (N), mean, SD, median, 25th and 75th percentiles, and minimum and maximum. Discrete variables will be summarized using counts and percentages.

Summaries will be provided for demographics, medical history, concomitant medications, and adverse events. For summaries of medical history, concomitant medications, and AEs, the Medical Dictionary for Regulatory Activities (MedDRA®) and the World Health Organization Drug dictionaries, as appropriate, will be used.

All data listings, summaries, and statistical analyses will be generated using SAS® Version 9.4 (or higher) or other validated software.

6. Efficacy analysis

As described in Section 2.3, the study has three hypotheses.

6.1. Primary outcome (Hypothesis 2)

Hypothesis 2: Overall >50% of symptom burden is nocebo rather than pharmacological.

For the trial, all participants receive a smartphone or, if they prefer, the application can be downloaded to their existing phone. Access to the phone will allow them to record real-time daily documentation of symptoms experienced on a visual analogue scale of 0-100. Participants will rate symptoms every day, with the daily scores averaged into a monthly score.

Each participant receives four months (4 × 28 days) each of no medication, placebo, and active medication (i.e, statin). We represent the individual participant's symptom score data as follows:

$$\begin{matrix} x_{0_1} & x_{p_1} & x_{s_1} \\ x_{0_2} & x_{p_2} & x_{s_2} \\ x_{0_3} & x_{p_3} & x_{s_3} \\ x_{0_4} & x_{p_4} & x_{s_4} \end{matrix}$$

$$\bar{x}_0 = \frac{\sum_{j=1}^{4} x_{0_j}}{4} = \frac{\sum_{j=1}^{4}\left(\sum_{i=1}^{28} x_{0_i}\right)/28)}{4}, \bar{x}_p = \frac{\sum_{j=1}^{4} x_{p_j}}{4} = \frac{\sum_{j=1}^{4}\left(\sum_{i=1}^{28} x_{p_i}\right)/28)}{4}, \bar{x}_s = \frac{\sum_{j=1}^{4} x_{s_j}}{4} = \frac{\sum_{j=1}^{4}\left(\sum_{i=1}^{28} x_{s_i}\right)/28)}{4}$$

$\bar{x}$- mean symptom score for no medication, placebo, statin, i-day 1 to 28 of treatment month, j – treatment month 1 to 4

We assume no carry-over effect. Thus, the estimated mean of the effect of nocebo is calculated as follows:

$$Mean\ nocebo\ effect = \sum_{n=1}^{N}\left(\frac{\bar{x}_{p_n} - \bar{x}_{0_n}}{\bar{x}_{s_n} - \bar{x}_{0_n}}\right)/N$$

N= number of study participants

Because the study participants are independent of each other, the variance of the estimated mean can be calculated as the as the sum of variances of the individual participants:

$$Variance\ of\ the\ mean\ nocebo\ effect = s^2 = \sum_{n=1}^{N} {s_n}^2 = \sum_{n=1}^{N} Var\left(\frac{\bar{x}_{p_n} - \bar{x}_{0_n}}{\bar{x}_{s_n} - \bar{x}_{0_n}}\right)$$

To calculate the variance of the estimate, we use a Taylor series approximation, which is a function of the variance of the numerator, variance of the denominator, and the covariance of the two:

1) $Var(numerator) = Var\left(\bar{x}_p - \bar{x}_0\right) = {s_p}^2 + {s_0}^2 - 2r_{s_p s_0} s_p s_0$

2) $Var(denominator) = Var\left(\bar{x}_s - \bar{x}_0\right) = {s_s}^2 + {s_0}^2 - 2r_{s_s s_0} s_s s_0$

3) $Cov(numerator,\ denominator) = cov(\bar{x}_p - \bar{x}_0,\ \bar{x}_s - \bar{x}_0) = cov(\bar{x}_p,\ \bar{x}_s) - cov(\bar{x}_p,\ \bar{x}_0) - cov(\bar{x}_0,\ \bar{x}_s) + cov(\bar{x}_0,\ \bar{x}_0) = cov(\bar{x}_p,\ \bar{x}_s) - cov(\bar{x}_p,\ \bar{x}_0) - cov(\bar{x}_0,\ \bar{x}_s) + s_0^2$

where, for example, $cov(\bar{x}_p, \bar{x}_s) = \frac{\sum_{i=1}^{4}(x_{p_i} - \bar{x}_p)(x_{s_i} - \bar{x}_s)}{4-1}$

4) $s_n^2 = Var\left(\frac{\bar{x}_p - \bar{x}_0}{\bar{x}_s - \bar{x}_0}\right) = \left(\frac{\bar{x}_p - \bar{x}_0}{\bar{x}_s - \bar{x}_0}\right)^2 \left(\frac{Var(\bar{x}_p - \bar{x}_0)}{(\bar{x}_p - \bar{x}_0)^2} + \frac{Var(\bar{x}_s - \bar{x}_0)}{(\bar{x}_s - \bar{x}_0)^2} - 2\frac{cov(\bar{x}_p - \bar{x}_0, \bar{x}_s - \bar{x}_0)}{(\bar{x}_p - \bar{x}_0)(\bar{x}_s - \bar{x}_0)}\right)$

s = standard deviation, s^2= variance, r = correlation

The Taylor's series approximation is based on asymptotic theory. Should the data not allow stable estimates of the components of the variance, we will use a bootstrapped estimate of the variance.

To calculate the 95% CI for the mean nocebo effect, the test statistic is $t = \sqrt{N}(\mu - \mu_0)/\sqrt{s^2}$

The null hypothesis is rejected if $t > t_{\alpha,N-1}$ where, in SAS, $t_{\alpha,N-1}$ is TINV(1-α, N-1);

In SAS, the p value associated with the test statistic T is PVAL=1-probt(abs(T), N-1) or PVAL=cdf('T', T, N-1).

The 95% confidence interval is $Mean\ nocebo\ effect \pm t_{\alpha/2,N-1}\sqrt{s^2}/\sqrt{N}$

6.1.1. Missing and partial data for primary outcome

For the calculation of mean symptom score for particular treatment (statin, placebo, no medication) missing scores (i < 28) will be handled by only using study months that have at least 10 of daily symptom scores non-missing. We will perform sensitivity analyses using different thresholds for non-missing scores (such as 14 and 16 non-missing scores) and compare the percentage of missing symptoms scores during the 'pill' months (statin or placebo) versus 'no pill' months. We will assess the temporal pattern of missing symptom scores by comparing the percentage of missing scores at the beginning of the study to the percentages at later study months.

The nocebo effect for an individual participant will be calculated only if he or she has non-missing symptom scores for at least one month of each treatment ($j \geq 1$). If the participant has not recorded any symptom score for one of the three treatments (j=0 for statin, placebo, or no pill) the nocebo effect cannot be calculated, and the primary endpoint analysis will exclude that participant.

6.2. Other efficacy outcomes

6.2.1. *Hypothesis 1*

Hypothesis 1: More than 30% of enrolled participants will complete the study.

1) Point estimate $\hat{p} = x/N$ where x is the number of participants who completed the study and N is the number of enrolled participants
2) Hypotheses: $H_0 : \hat{p} = p_0$ *and* $H_A = \hat{p} > p_0$ *where* $p_0 = 0.3$
3) Test statistic $z = \frac{\hat{p} - p_0}{\sqrt{p_0(1-p_0)/N}}$
4) Reject null hypothesis if $z > z_\alpha$, *where* $z_{0.05} = 1.645$
5) 95% confidence interval: $\hat{p} \pm z_{\alpha/2}\sqrt{\hat{p}(1-\hat{p})/N} = \hat{p} \pm 1.96\sqrt{\hat{p}(1-\hat{p})/N}$

6.2.2. *Hypothesis 3*

Hypothesis 3: At six months after completion of the study, at least 50% of the participants will either be taking statins or have declined statins for reasons other than perceived side effects. This hypothesis will be tested in the same way as Hypothesis 1 above but setting $p_0 = 0.5$.

7. Characteristics of the population

7.1. Demographics and baseline characteristics

Quantitative variables will be summarized using the number of subjects (N), mean, SD, median, 25th and 75th percentiles, and minimum and maximum. Qualitative variables will be summarized using counts and percentages.

The following demographic and baseline characteristics will be summarized: age, gender, height, weight, ethnicity, and past use of statin. Blood pressure and selected biochemistry laboratory measurements reported as well.

Age in years will be calculated as the integer portion of the following:

[(Date of randomization- Date of birth) + 1] / 365.25.

Unless otherwise stated, percentages will be calculated relative to the number of subjects randomized.

7.2. Concomitant medications

Information on concomitant medication may be summarized by generic name as reported on the concomitant medication CRF. The number and percentage of subjects who took at least one drug within each generic type will be presented. Subjects will be counted only once if they take the same generic medication more than once.

7.3. Medical history

Medical history will be coded using the MedDRA and summarized by system organ class (SOC) and preferred term (PT). Medical history may be sorted by descending overall frequency, by SOC and PT, in the summary tables.

8. Protocol deviations

Important protocol deviations will be summarized by the category reported on the CRF form and sorted by descending overall frequency

9. Adverse events

Adverse events (AEs) are monitored throughout the study and documented on the appropriate AE form. They are coded using the MedDRA dictionary by system organ class (SOC) and preferred term (PT); they will be classified by seriousness, severity, and relation to study medications.

Appendix 8: Ethics approval letter

NHS
Health Research Authority
London - Brent Research Ethics Committee
80 London Road
Skipton House
London
SE1 6LH

Telephone: 020 7972 2554

04 November 2015

Prof Darrel Francis
Professor of Cardiology
Imperial College London
Hammersmith Hospital, Du Cane Road
London
London
W12 OHS

Dear Prof Francis

Study title:	**Self-Assessment Method for Statin side-effects Or Nocebo (SAMSON) trial.**
REC reference:	**15/LO/1761**
Protocol number:	**15SM2947**
EudraCT number:	**2015-004109-18**
IRAS project ID:	**165971**

The Research Ethics Committee reviewed the above application at the meeting held on 26 October 2015. Thank you for attending to discuss the application.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Ms Julie Kidd, nrescommittee.london-brent@nhs.net . Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below. .

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Appendix 9: Dates of regulatory and ethical approval were granted to recruit participants to the trial.

Date of Ethical approval	04-Nov-2015
Date of MHRA Approval	05-Nov-2015
Date of Portfolio Adoption	17-Nov-2015
Date of R&D approval	10-Mar-2016

Appendix 10: Details of amendments to ethics and MHRA approval during the trial

Amendment Type & Number	Purpose of Amendment	Rationale
Substantial amendment 1	This substantial amendment sought permission from the REC to edit the wording of the inclusion and exclusion criteria to clarify eligibility criteria and also to clarify a minor point of the trial procedure. **Trial protocol updated to Version: 1.1, dated: 11th December 2015.**	Clarify trial procedure
Substantial amendment 2	This substantial amendment sought permission to advertise SAMSON on Facebook and Twitter	Facilitate recruitment
Substantial amendment 3	This substantial amendment sought permission from the REC for paid advertising of the SAMSON trial on the social media website Facebook.	Facilitate recruitment
Substantial amendment 4	This substantial amendment sought permission from the REC to be able to include the study team's contact details in relevant health professional publications submitted about the trial to allow readers to refer willing patients.	Facilitate recruitment
Substantial amendment 5	This substantial amendment sought approval from the REC of a new poster (version 1.0 dated: 21st March 2017) to advertise the pilot study. It also notified the REC that the study team would be applying to the HRA to come under the HRA approval because the trial team intended to open more Patient Identifying Centres (PIC) listed on the original REC application that was submitted prior to 31st March 2016). This substantial amendment also sought permission of the REC for an edit to the current Facebook adverts and landing page.	Facilitate recruitment

Amendment Type & Number	Purpose of Amendment	Rationale
HRA approval	This amendment sought permission for the study to come under HRA approval	Facilitate recruitment
Non substantial amendment 1 and 2	These non-substantial amendments were submitted to the HRA to list all GP practices potentially to be approached in Surrey and Sussex for the SAMSON trial because previously had approval from the Sussex Research Consortium and this had dissolved, and subsequently individual GP practices were to confirm their capacity and capability. In addition, a minor amendment to the wording of the SAMSON Trial poster to add clarity and readability was sought.	Facilitate recruitment
Substantial amendment 6	This substantial amendment sought permission of the REC for the approval of a new recruitment video about the SAMSON trial	Facilitate recruitment
Substantial amendment 7	This substantial amendment sought the approval of the REC for recruitment through Heart UK.	Facilitate recruitment
Substantial amendment 8	This substantial amendment sought permission to extend the trial duration to Sept 2020 as the research nurse on the trial had a no-cost extension to her contract. In addition, this substantial amendment sought permission to advertise through the British Heart Foundation, request telephone consent for interviews for the pilot study and request permission to undertake a personality sub-study. **Trial protocol updated to Version: 1.2 Dated: 1st August 2018**	Extend trial duration, facilitate recruitment and explore generalisability of the trial results
Substantial amendment 9	This substantial amendment sought approval from the competent authority (MHRA) for an update to the SmPC.	SmPC update.
Non substantial amendment 3	Due to Covid-19 protocol updated to state that End of Study visits to be undertaken by telephone rather than face-to-face **l protocol updated to Version: 1.3 Dated: 6th April 2020.**	Clarify trial procedure.
Substantial amendment 10	This substantial amendment sought the permission of the REC to update the protocol to explain the deviation from the statistical analysis plan and protocol. Assumptions	Clarify trial procedure and analysis.

	about data were violated and so statistical analysis deviated from SAP and study protocol. **Trial protocol updated to Version: 1.4 Dated: 10th April 2020.**	

Appendix 11: SAMSON Phone Scores User Requirement Specification

Author: Dr James Howard

Overall set-up:
The phone app used by SAMSON is a web page which is saved to the user's phone. It uses two free open-source systems to work - a database called CouchDB and a software collection called Hoodie. As it is coded in HTML and JavaScript it can run on any computer or smartphone with a modern browser. The server is run by a well-respected multinational server provider, Linode,

Installation:

To install the app, users navigate to the website https://samson.icch.london and 'add' it to their home screen. If they then navigate to the app and log-in using their username and password, they can log in to the questionnaire. In the background, the app will be 'cached' (saved to the user's phone). This means it can be used even when an internet connection is not available (or if the server is down). Their login information will be saved for two years unless they remove the app, reset their phone, or choose to sign out.

Usage:

The app can be used on any desktop, laptop, tablet or smartphone with a modern browser. By accessing it either through their browser or home screen (see installation above) they can log in to their account. Typically, the research staff will do this for them the first time, and the phone will save this information for future use for up to two years.
After logging in they will be reminded of which month of the trial they are on and be asked the two research questions.
After this they are given a message confirming submission is successful.
If no internet connection is present at this time, the scores will be saved. The users will not be told of this (no error message will display), but the data will upload automatically next time the application is run.

Data upload:

The responses to the two research questions are sent to the server running at https://samson.icch.london via SHA-2 encryption. This is a very secure encryption system which is an industry standard for encrypting secure web pages. This means that the data were intercepted between the user's phone and the server it would be absolutely unintelligible and would require many hundreds of years to decrypt using computers of today's capabilities.

Data storage:

No patient-identifiable information is present on either the users' phones or the server. In the unlikely event the security on either the user's phone or web server were compromised, not breaches of confidentiality would occur.

Data is stored on the user's phone. This data consists of

- The phone application
- The user's username (anonymised trial ID)
- The user's password (chosen by trial staff)
- The data the user started the trial
- Previous responses

No patient-identifiable information or information about other users is stored on the phone.

Data is also stored on the server. This data consists of

- Each user's username (anonymised trial ID)
- Each user's password (chosen by trial staff; encrypted)
- The date each user starts the trial
- The responses for each patient to date

Data download:

Data on the server must be sent to Imperial College for processing. This is performed by the automatic execution of a small program which outputs a

spreadsheet of the preceding day's data. This is sent securely to Imperial College. The only information included in this spreadsheet are the users' anonymised trial IDs, the date, and the responses to the two research questions.

Data backup:
Daily and weekly backups are automatically made by the server provider.

Data management team:
Dr James Howard has user access and is responsible for the above day-to-day data management. In addition, Dr Matthew Shun-Shin has additional user access and is the standby data manager in the event Dr James Howard is unavailable.

Appendix 12: Test script results summary

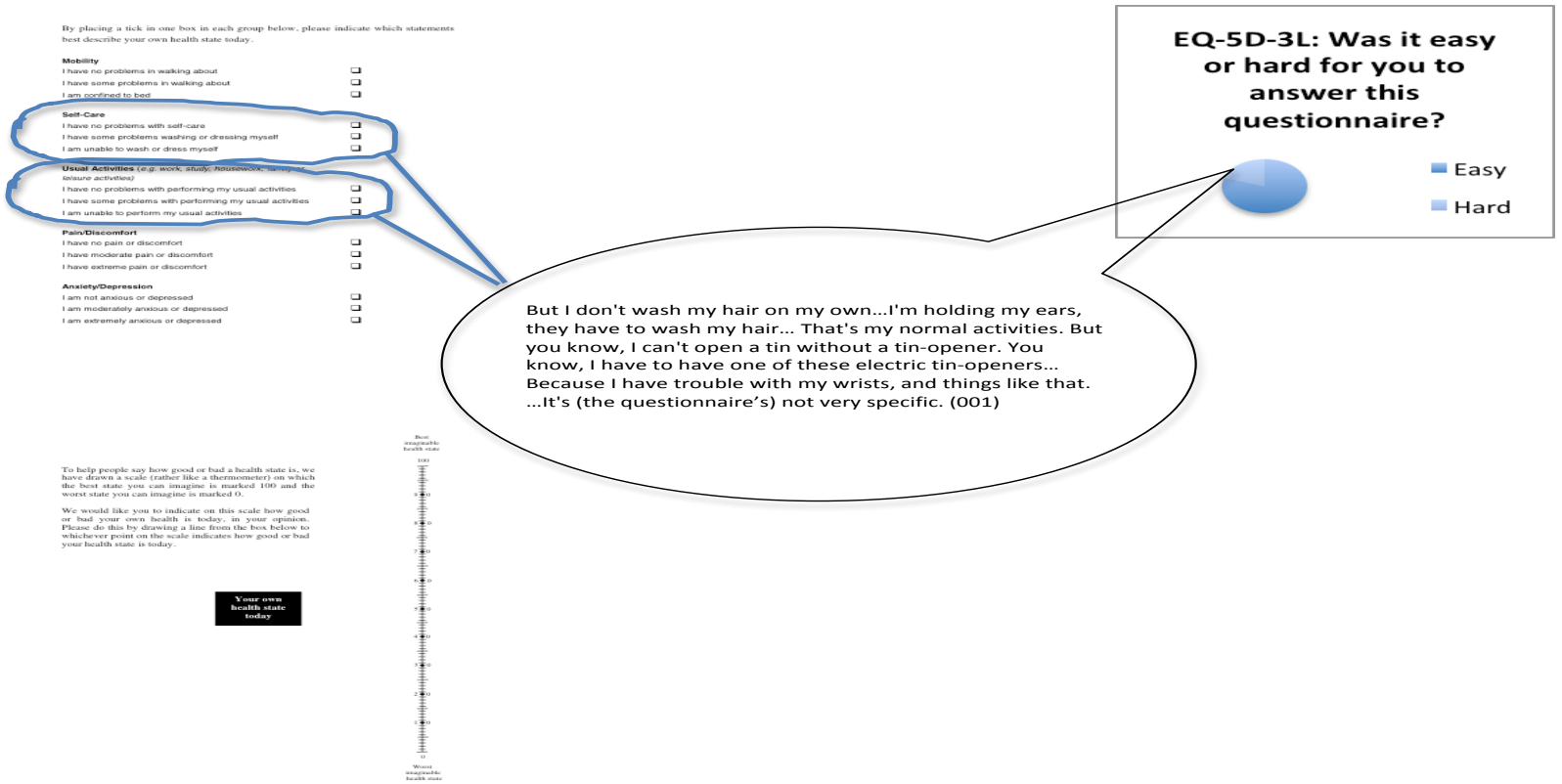
18. Test Script Results Summary

TS#	Test Objective	Result	Comments
TS01	User Access and Home Page	☐ Pass ☐ Fail	PASS
TS02	System Screening and System Enrolment	☐ Pass ☐ Fail	PASS
TS03	Entering Patient Data	☐ Pass ☐ Fail	PASS except 3.17 did not highlight when left blank
TS04	Randomisation	☐ Pass ☐ Fail	Version 1: FAIL on 4.6, 4.7 and awaiting email confirmation of 4.8 Version 2: PASS
TS05	Uploading data of daily phone scores	☐ Pass ☐ Fail	Version 1: Pending action from SAMSON study before this can be tested. Version 2: PASS
TS06	Answering Queries	☐ Pass ☐ Fail	Version 1: Fail - 6.2 Query does not appear in closed or answered. Version 2: PASS
TS07	Adverse Events and Concomitant Medications	☐ Pass ☐ Fail	Version 1: FAIL wrong query generated 7.8 There is no other option for route of admin of conmeds, we require other and free text for other, please specify. Awaiting email confirmations to pass certain sections and wrong query raised for 7.8. Version 2: PASS
TS08	Study Completion Forms	☐ Pass ☐ Fail	PASS
TS09	Closing and Raising Queries	☐ Pass ☐ Fail	PASS

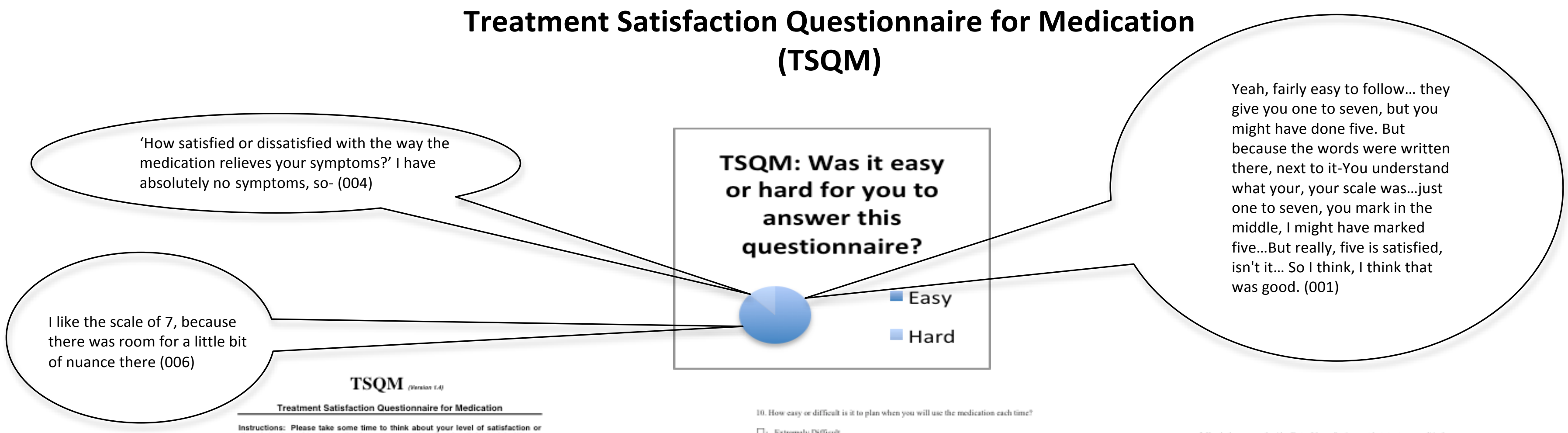
TS#	Test Objective	Result	Comments
TS10	Monitoring	□ Pass □ Fail	PASS
TS11	Signatures	□ Pass □ Fail	PASS
TS12	Reporting	□ Pass □ Fail	PASS

Appendix 13: EQ-5D-3L questionnaire, with pie-chart showing percentage of participants who found questionnaire easy to complete and comments made about questionnaires that were hard

EQ-5D-3L



Appendix 14*:* TSQM questionnaire, with pie-chart showing percentage of participants who found questionnaire easy to complete and comments made about the questionnaire.



TSQM *(Version 1.4)*

Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last two to three weeks, or since you last used it.* For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

4. As a result of taking this medication, do you experience any side effects at all?

☐1 Yes
☐0 No (if No, then please skip to Question 9)

[Clinical Trial Version] 1

10. How easy or difficult is it to plan when you will use the medication each time?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

11. How convenient or inconvenient is it to take the medication as instructed?

☐1 Extremely Inconvenient
☐2 Very Inconvenient
☐3 Inconvenient
☐4 Somewhat Convenient
☐5 Convenient
☐6 Very Convenient
☐7 Extremely Convenient

12. Overall, how confident are you that taking this medication is a good thing for you?

☐1 Not at All Confident
☐2 A Little Confident
☐3 Somewhat Confident
☐4 Very Confident
☐5 Extremely Confident

13. How certain are you that the good things about your medication outweigh the bad things?

☐1 Not at All Certain
☐2 A Little Certain
☐3 Somewhat Certain
☐4 Very Certain
☐5 Extremely Certain

14. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

[Clinical Trial Version] 3

5. How bothersome are the side effects of the medication you take to treat your condition?

☐1 Extremely Bothersome
☐2 Very Bothersome
☐3 Somewhat Bothersome
☐4 A Little Bothersome
☐5 Not at All Bothersome

6. To what extent do the side effects interfere with your physical health and ability to function (i.e., strength, energy levels, etc.)?

☐1 A Great Deal
☐2 Quite a Bit
☐3 Somewhat
☐4 Minimally
☐5 Not at All

7. To what extent do the side effects interfere with your mental function (i.e., ability to think clearly, stay awake, etc.)?

☐1 A Great Deal
☐2 Quite a Bit
☐3 Somewhat
☐4 Minimally
☐5 Not at All

8. To what degree have medication side effects affected your overall satisfaction with the medication?

☐1 A Great Deal
☐2 Quite a Bit
☐3 Somewhat
☐4 Minimally
☐5 Not at All

9. How easy or difficult is it to use the medication in its current form?

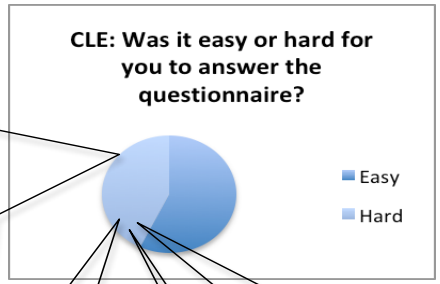
☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

[Clinical Trial Version] 2

Appendix 15: CLE questionnaire, with pie-charts showing percentage of participants who found questionnaire easy to complete in general and in regard to response choice and recalling events in the last month with comments.

Confounding Life Events Questionnaire (CLE)

I suppose the bullying one or the victimisation of feelings or social isolation, I absolutely have not had anything like that, but …it made me feel quite vulnerable…if I had, I think I'd feel embarrassed to write it down (006)



Time off for relaxation, does that mean an hour off or two hours off or two days off? It's a bit vague. (009)

You know, if you were ticking all those boxes, when you got to the end of it you'd be thinking, you know, "It's understandable that this person's a complete wreck (004)

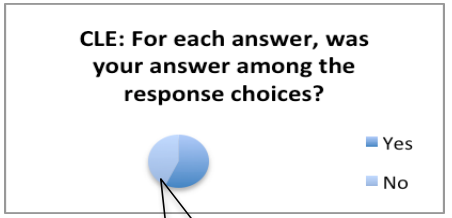
You should clarify 'change in routine other than holiday' (005)

Confounding Life Events Questionnaire

This questionnaire is designed to assess life events over the last 1 month that might have had a positive or negative impact on your mental or physical well-being. Please answer the questions in terms of events that have taken place in your life since you began Month _ of the SAMSON study.

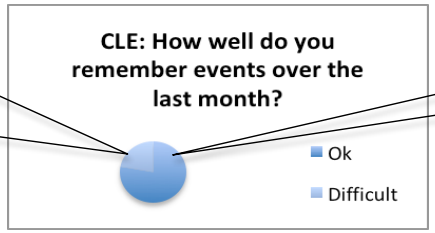
1. In the last **one month** I have experienced the death or serious illness/injury of a close friend or family member?
   Yes □ No □
2. In the last **one month** I have had difficulty with a close relationship?
   Yes □ No □
3. In the last **one month** I have suffered bullying, victimization of feelings of social isolation?
   Yes □ No □
4. In the last **one month** I have lost my job or experienced financial problems?
   Yes □ No □
5. In the last **one month** I have had significant worsening of my physical or mental well-being?
   Yes □ No □
6. In the last **one month** I have experienced another seriously upsetting event, accident or situation?
   Yes □ No □
7. In the last **one month** I have had a holiday or time-off for relaxation?
   Yes □ No □
8. In the last **one month** I have had significant changes to my usual routine?
   Yes □ No □
9. In the last **one month** I have had a significant personal achievement?
   Yes □ No □
10. In the last **one month** I have had significant improvement in my physical or mental well-being?
    Yes □ No □

Thank you for completing this questionnaire.



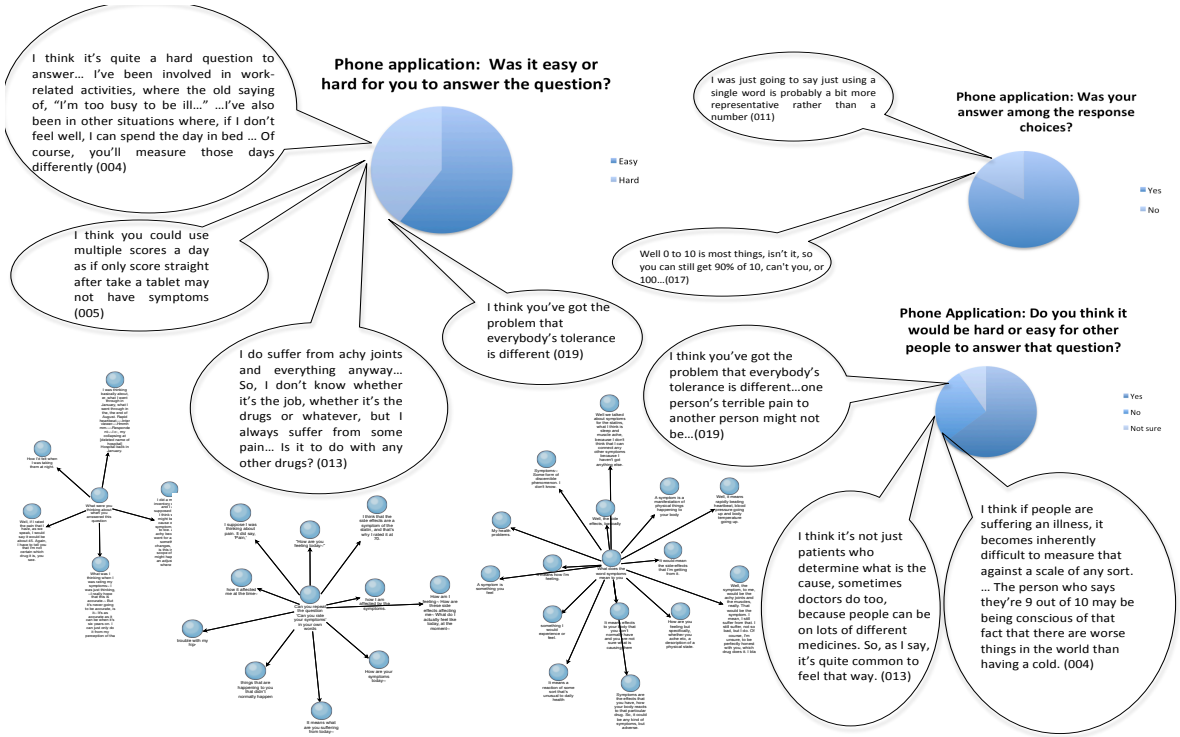
I think it's probably quite difficult, because some of the questions are quite intrusive and if you are feeling negative or depressed about a life event you might not necessarily wish to put it into a binary formal of yes or no. (011)

there will be an age situation here: When my dad got into his 80s he would tell us the same thing three times in the same hour. You know, and just a product of getting older and being a bit more forgetful. But, for the majority of people on your trial, who I'm going to guess are probably in sort of middle age up into their 60s and whatever, that they're perfectly reasonable questions. (004)



I think I would forget if it was more than month. I would have concern if somebody could not keep track of events over one month. No difficulty answering this questionnaire (005)

Appendix 16: Pie-charts showing percentage of participants who found phone application easy to complete in general and in regard to response choice. Spider graphs exploring what participants understand by the wording 'symptoms



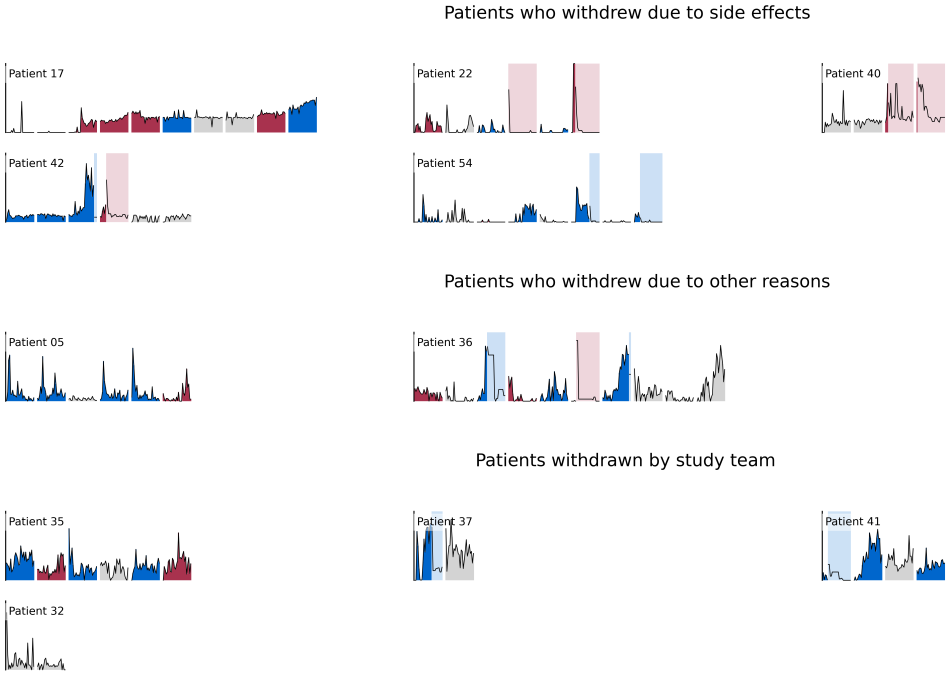
Appendix 17: Overview of recruitment by approach and outcome including reasons for non-inclusion during pre-screening

	Clinician referral from outpatient clinic	Self-referral	Onward referral from other trials	Facebook advertising	Mass GP mail outs	Source unknown	**Total**
n	114	83	7	368	157	14	**743**
No response	7	N/A	0	N/A	N/A	0	**7**
No reply following initial contact	3	N/A	0	146	8	0	**157**
Not target population (abandoned statins because of side effects arising within 2 weeks)							
Never taken statins	4	1	0	4	20	2	**31**
No side effects	1	4	0	11	10	0	**26**
Symptoms took > 2 weeks	4	17	1	10	0	2	**34**
Still on statins despite side effects	22	13	1	122	22	0	**180**
Total non-target population	31	35	2	147	52	4	**271**
Excluded at pre-screening because of exclusion criteria							
Chronic pain condition	1	1	0	4	2	0	**8**
Time to onset unknown	1	1	0	0	0	1	**3**
Raised Liver Enzymes	1	1	0	0	1	0	**3**
Acute mental health issue	0	0	0	1	1	0	**2**
Raised CK	0	0	0	2	0	0	**2**
Fenofibrate	1	0	0	0	0	0	**1**
Reason not recorded	1	0	0	0	0	0	**1**
Female attempting to conceive a child	1	0	0	0	0	0	**1**
Communication difficulties	1	0	0	1	1	0	**3**

	Clinician referral from outpatient clinic	Self-referral	Onward referral from other trials	Facebook advertising	Mass GP mail outs	Source unknown	**Total**
Total excluded at pre-screening	7	3	0	8	5	1	**24**
Declined to attend screening					0		
Cancelled appointment	3	4	0	0	0	0	**7**
No reason specified	22	6	3	11	52	8	**102**
On PCSK9	2	0	0	1	0	0	**3**
Not willing to restart a statin	9	3	0	7	9	1	**29**
Anxiety about travelling to site	0	0	0	1	0	0	**1**
Too nervous to take part	1	0	0	0	0	0	**1**
Certain statins were cause of side effects	0	0	0	3	0	0	**3**
Denies responding to trial	0	0	0	2	0	0	**2**
Too busy	5	2	0	14	10	0	**31**
Too old	0	0	0	0	6	0	**6**
Satisfied with current regime	0	0	0	0	1	0	**1**
Poor mobility	1	0	0	0	1	0	**2**
On another study	0	0	0	1	0	0	**1**
Would only participate if paid	0	0	0	2	0	0	**2**
Lives too far away	0	0	0	23	1	0	**24**
Believes would not complete the 12-months of the trial	0	0	0	1	0	0	**1**
Can control cholesterol with diet	0	0	0	0	2	0	**2**

	Clinician referral from outpatient clinic	Self-referral	Onward referral from other trials	Facebook advertising	Mass GP mail outs	Source unknown	**Total**
Fed up with doctors poking at me because of my hereditary problem	0	0	0	0	1	0	**1**
Recent hip replacement	0	0	0	0	1	0	**1**
Statins don't work for him	0	0	0	0	1	0	**1**
Takes too many tablets already	0	0	0	0	1	0	**1**
Total declining to attend pre-screening	43	15	3	66	86	9	**222**
Attended for screening							
Screen failed	1	0	0	1	0	0	**2**
Randomised	22	30	2	0	6	0	**60**
Total attending screening	23	30	2	1	6	0	**62**

Appendix 18: Data for withdrawers:



Every daily score in each of the 11 patients who were randomized but did not complete the 12-month trial protocol (labelled by their trial number). The vertical axes represent symptom scores; the horizontal axes represent time (days separated into 12 monthly intervals). Symptom intensity bars are coloured grey in no-tablet months, blue in placebo months and red in statin months. Lighter shaded regions indicate that patients have stopped tablets early for that month due to intolerable symptoms (Howard et al. 2021, appendix p.8)

Appendix 19: The four multi-level models (as published in NEJM)

Model	Dev*	ΔDev	p	Within month variance	Between month within subject variance	Between subject variance (intercept)	Between subject variance (slope)	Correlation between adjacent days within month
Unconditional	143258	---	---	111.4	119.9	132.2	---	---
Fixed effect of treatment	143171	87.1	< 0.001	111.4	103.3	134.1	---	---
Add random effect of treatment	143167	4.6	0.032	111.4	96.4	131.6	9.5	---
Adjust for autoregressive effect within study months (AR1 type autocorrelation)	132980	10189	< 0.001	137.6	64.7	130.8	9.0	0.714

The deviances of the four multilevel models assessed. The deviance was calculated as the -2Loglikelihood. P values were interpreted using a Chi-square distribution with.

Appendix 20: Adverse events by participant

Pt. ID	AE No.	AE description	Onset Date	Relatedness	Expectedness	Severity
1001	1	Indigestion (abdominal pain upper)	17-JUN-16	Possibly	Expected	2=Moderate
	2	Bloatedness	02-FEB-17	Possibly	Unexpected	1=Mild
	3	Flatulence	02-FEB-17	Possibly	Expected	1=Mild
	4	Worsening bloatedness	06-FEB-17	Possibly	Unexpected	1=Mild
	5	Indigestion (abdominal pain upper)	06-FEB-17	Possibly	Expected	1=Mild
	6	Abdominal pain	01-MAR-17	Possibly	Expected	1=Mild
	7	Diarrhoea	01-MAR-17	Possibly	Expected	1=Mild
	8	Diarrhoea	16-APR-17	Unlikely	Unexpected	1=Mild
	9	Bloatedness	16-APR-17	Unlikely	Unexpected	1=Mild
	10	Flatulence	16-APR-17	Unlikely	Unexpected	1=Mild
	11	Weight gain	15-FEB-17	Unlikely	Expected	1=Mild
	12	Myalgia in hip	17-JUN-16	Possibly	Expected	2=Moderate
	13	Arthralgia in hip	17-JUN-16	Possibly	Expected	2=Moderate
	14	Myalgia	09-AUG-16	Possibly	Expected	2=Moderate
	15	Arthralgia	15-JAN-17	Possibly	Expected	1=Mild
	16	Myalgia	15-JAN-17	Possibly	Expected	1=Mild
	17	Worsening Arthralgia	06-FEB-17	Possibly	Expected	1=Mild
	18	Arthralgia	30-MAR-17	Possibly	Expected	1=Mild
	N	18	18	18	18	18
1002	1	Chest pain	24-JUN-17	Unlikely	Unexpected	2=Moderate
	2	Common cold	23-DEC-16	Unlikely	Unexpected	1=Mild
	N	2	2	2	2	2
1003	1	Sore eyes	27-JUN-17	Unlikely	Unexpected	2=Moderate
	2	Flushing	27-JUN-17	Unlikely	Unexpected	2=Moderate
	3	'Influenza'	31-JAN-17	Unlikely	Unexpected	1=Mild
	4	Common Cold	07-FEB-17	Unlikely	Unexpected	2=Moderate
	5	Muscular cramp	10-MAY-17	Possibly	Expected	1=Mild
	6	Headache	27-JUN-17	Possibly	Expected	2=Moderate
	7	Anxiety	02-AUG-16	Unlikely	Unexpected	2=Moderate
	N	7	7	7	7	7
1004	1	Swallowing difficulty	01-SEP-16	Possibly	Unexpected	1=Mild
	2	Loose bowel movements	01-SEP-16	Possibly	Unexpected	1=Mild
	3	Pain in lower body (lower abdomen, back and thighs)	01-SEP-16	Possibly	Unexpected	2=Moderate

	4	Worsening of lower body pain (abdomen, back and thighs)	25-APR-17	Unlikely	Unexpected	2=Moderate
	5	Lack of balance	01-SEP-16	Possibly	Unexpected	1=Mild
	6	Fatigue	01-SEP-16	Possibly	Expected	1=Mild
	7	Low red blood cell count	16-JUN-17	Unlikely	Unexpected	2=Moderate
	8	Low blood calcium	16-JUN-17	Unlikely	Unexpected	2=Moderate
	9	Memory Loss	01-SEP-16	Possibly	Expected	1=Mild
	10	Lack of concentration	01-SEP-16	Possibly	Unexpected	1=Mild
	11	Disorientation	01-SEP-16	Possibly	Unexpected	1=Mild
	12	Insomnia	01-SEP-16	Possibly	Expected	1=Mild
	13	Poor urine flow	01-SEP-16	Possibly	Unexpected	1=Mild
	14	Enlargement of kidney stone (Right side)	01-APR-17	Not related	Unexpected	1=Mild
	15	Migraine	23-OCT-16	Possibly	Unexpected	1=Mild
	16	Increasing frequency of migraines	01-DEC-16	Not related	Unexpected	2=Moderate
	N	16	16	16	16	16
1005	1	Pancreatitis	11-APR-17	Not related	Expected	3=Severe
	2	Urinary tract infection	27-FEB-17	Unlikely	Unexpected	2=Moderate
	3	Urinary tract infection	24-APR-17	Not related	Unexpected	4=Life threatening or disabling
	4	Depression	01-DEC-16	Possibly	Expected	2=Moderate
	5	Urinary tract infection	30-OCT-16	Unlikely	Unexpected	2=Moderate
	6	Laparoscopic cholecystectomy and cholangiogram	02-MAY-17	Not related	Unexpected	2=Moderate
	N	6	6	6	6	6
1006	1	Lethargy	15-JUL-17	Possibly	Expected	1=Mild
	2	Rhinitis	01-NOV-16	Not related	Unexpected	1=Mild
	3	Myalgia (calves and toes)	15-JUL-17	Possibly	Expected	1=Mild
	4	Myalgia	16-AUG-17	Possibly	Expected	1=Mild
	5	Headache	15-JUL-17	Possibly	Expected	1=Mild
	6	Breathlessness	01-NOV-16	Not related	Unexpected	1=Mild
	7	Common Cold	31-JAN-17	Unlikely	Unexpected	2=Moderate
	8	Cough	01-DEC-16	Possibly	Unexpected	1=Mild
	9	Common Cold	11-FEB-17	Unlikely	Unexpected	1=Mild

	10	Nasopharyngitis	15-JUL-17	Possibly	Expected	1=Mild
	11	Nasal congestion	16-AUG-17	Possibly	Expected	1=Mild
	12	Nasal congestion	27-OCT-17	Unlikely	Unexpected	1=Mild
	13	Worsening of nasal congestion	27-OCT-17	Not related	Unexpected	1=Mild
	N	13	13	13	13	13
1007	1	Nausea	01-DEC-16	Possibly	Expected	1=Mild
	2	Exacerbation of nausea	20-MAR-17	Unlikely	Expected	1=Mild
	3	nausea	01-JUL-17	Possibly	Expected	1=Mild
	4	Exacerbation of nausea	13-AUG-17	Possibly	Expected	1=Mild
	5	Nausea	01-NOV-17	Unlikely	Expected	1=Mild
	6	Arthralgia elbow	24-DEC-16	Possibly	Expected	1=Mild
	7	Myalgia	20-MAR-17	Unlikely	Expected	1=Mild
	8	Cataract removal (Left eye)	15-DEC-16	Not related	Unexpected	2=Moderate
	9	Cataract removal (right eye)	02-DEC-16	Not related	Expected	2=Moderate
	10	Transient ischaemic attack	15-DEC-17	Not related	Unexpected	3=Severe
	N	10	10	10	10	10
1009	1	Exacerbation of Rheumatoid Arthritis	25-SEP-17	Unlikely	Unexpected	2=Moderate
	2	Common cold	01-DEC-17	Unlikely	Expected	2=Moderate
	3	Myalgia	01-DEC-17	Possibly	Expected	2=Moderate
	4	Hypotension	18-MAY-17	Not related	Unexpected	2=Moderate
	N	4	4	4	4	4
1010	1	Aortic Regurgitation	18-DEC-17	Unlikely	Unexpected	1=Mild
	2	Dizziness	03-MAR-18	Possibly	Expected	2=Moderate
	3	Itchy ear	04-MAR-18	Unlikely	Unexpected	2=Moderate
	4	Floater in eye	06-APR-18	Unlikely	Unexpected	1=Mild
	5	'Removal of film from eye'	23-APR-18	Unlikely	Unexpected	2=Moderate
	6	Malaise due to ?virus	08-SEP-17	Unlikely	Unexpected	1=Mild
	7	Hay fever	01-JUN-17	Unlikely	Unexpected	2=Moderate
	8	Anaphylactic reaction to ferrous infusion	02-MAY-18	Not related	Unexpected	3=Severe
	9	Hayfever	01-MAY-18	Unlikely	Unexpected	1=Mild
	10	Chest Infection	01-OCT-17	Unlikely	Unexpected	1=Mild
	11	Common Cold	09-SEP-17	Unlikely	Unexpected	2=Moderate
	12	Common cold	10-APR-18	Unlikely	Unexpected	1=Mild

	13	Midgee Bites	01-JUN-17	Not related	Unexpected	2=Moderate
	14	Hypermobility Syndrome	14-APR-19	Not related	Unexpected	2=Moderate
	15	Leg pain	01-AUG-17	Possibly	Expected	1=Mild
	16	myalgia	01-OCT-17	Possibly	Expected	1=Mild
	17	Myalgia	23-MAR-18	Possibly	Expected	2=Moderate
	N	17	17	17	17	17
1011	1	Inflamed eye	04-AUG-17	Unlikely	Unexpected	2=Moderate
	2	Eructation	03-JUL-17	Possibly	Expected	1=Mild
	3	Indigestion	27-JUL-17	Possibly	Expected	2=Moderate
	4	Diarrhoea	18-SEP-17	Unlikely	Expected	1=Mild
	5	Common cold	03-DEC-17	Unlikely	Expected	2=Moderate
	6	Common Cold	19-MAR-18	Unlikely	Unexpected	1=Mild
	7	Shoulder pain (from mechanical fall)	15-FEB-18	Not related	Unexpected	1=Mild
	8	Anxiety	15-DEC-17	Unlikely	Unexpected	2=Moderate
	9	Sleep disturbance	29-JAN-18	Possibly	Expected	1=Mild
	10	Anxiety	29-DEC-17	Unlikely	Unexpected	1=Mild
	11	Cough	01-MAR-18	Unlikely	Unexpected	1=Mild
	12	Cough	03-DEC-17	Unlikely	Unexpected	2=Moderate
	13	Removal of polyps from bowel	16-OCT-17	Unlikely	Unexpected	1=Mild
	N	13	13	13	13	13
1012	1	diarrhoea	05-AUG-17	Possibly	Expected	1=Mild
	2	Diarrhoea	15-OCT-17	Possibly	Expected	1=Mild
	3	Constipation	01-NOV-17	Possibly	Expected	1=Mild
	4	Diarrhoea	03-FEB-18	Possibly	Expected	1=Mild
	5	Constipation	22-MAR-18	Possibly	Expected	1=Mild
	6	Tendonitis	05-AUG-17	Possibly	Expected	1=Mild
	7	Multiple System Atrophy	26-MAY-18	Not related	Unexpected	4=Life threatening or disabling
	8	Cough	01-MAR-18	Possibly	Unexpected	1=Mild
	9	Common cold	19-FEB-18	Unlikely	Unexpected	2=Moderate
	N	9	9	9	9	9
1015	1	diarrhoea	13-APR-18	Possibly	Expected	1=Mild
	2	Fatigue	14-JUL-17	Possibly	Expected	1=Mild
	3	Hayfever	15-MAY-18	Unlikely	Expected	2=Moderate
	4	Myalgia	14-JUL-17	Possibly	Expected	1=Mild
	5	Myalgia	04-NOV-17	Possibly	Expected	2=Moderate
	6	myalgia	14-JAN-18	Possibly	Expected	2=Moderate
	7	Myalgia	09-FEB-18	Possibly	Expected	2=Moderate
	8	Myalgia	17-APR-18	Possibly	Expected	2=Moderate
	9	Cough	16-MAY-18	Unlikely	Expected	2=Moderate

	10	Prickly heat	13-APR-18	Unlikely	Unexpected	1=Mild
	N	10	10	10	10	10
1016	1	Constipation	12-MAR-18	Possibly	Expected	1=Mild
	2	Urinary tract infection	20-OCT-17	Unlikely	Expected	2=Moderate
	3	Urinary tract infection	15-NOV-17	Unlikely	Unexpected	2=Moderate
	4	Urinary tract infection	23-MAR-18	Unlikely	Unexpected	2=Moderate
	5	Mild myalgia	08-JAN-18	Possibly	Expected	1=Mild
	6	Myalgia	12-MAR-18	Possibly	Expected	1=Mild
	7	Myalgia	01-JUN-18	Possibly	Expected	1=Mild
	8	Joint stiffness	01-JUN-18	Possibly	Expected	1=Mild
	9	Headaches	12-MAR-18	Possibly	Expected	2=Moderate
	10	Percutaneous Coronary intervention (3 stents)	30-NOV-17	Unlikely	Unexpected	1=Mild
	11	Hypertension	27-SEP-17	Unlikely	Unexpected	2=Moderate
	N	11	11	11	11	11
1017	1	Abdominal discomfort	23-OCT-17	Possibly	Expected	2=Moderate
	2	Chest infection	28-JAN-18	Unlikely	Unexpected	1=Mild
	3	Cramps in neck	31-DEC-17	Possibly	Expected	1=Mild
	4	Headache	19-MAR-18	Unlikely	Expected	2=Moderate
	5	Headache	27-APR-18	Unlikely	Expected	1=Mild
	6	sore throat	01-OCT-17	Unlikely	Unexpected	1=Mild
	7	Sore throat	24-DEC-17	Unlikely	Unexpected	1=Mild
	8	Common Cold	24-DEC-17	Unlikely	Unexpected	1=Mild
	9	Exacerbation of alopecia	28-NOV-17	Possibly	Expected	1=Mild
	N	9	9	9	9	9
1018	1	Diarrhoea	29-JUN-18	Not related	Unexpected	2=Moderate
	2	Vomiting	29-JUN-18	Not related	Unexpected	2=Moderate
	3	Tiredness	25-SEP-17	Possibly	Expected	1=Mild
	4	Left sided facial ache (headache)	25-SEP-17	Possibly	Expected	1=Mild
	5	Physical weakness	01-DEC-17	Unlikely	Unexpected	2=Moderate
	6	Fatigue	17-APR-18	Possibly	Expected	2=Moderate
	7	Myalgia (amlodipine)	31-MAY-18	Possibly	Expected	2=Moderate
	8	Fatigue	01-DEC-17	Unlikely	Unexpected	2=Moderate
	9	Low vitamin D	20-DEC-17	Unlikely	Unexpected	2=Moderate
	10	Myalgia (bilaterally in waist)	09-FEB-18	Possibly	Expected	2=Moderate

	11	Myalgia (bilaterally waist)	06-MAR-18	Possibly	Expected	2=Moderate
	12	Throbbing pain in left arm	25-MAR-18	Unlikely	Unexpected	1=Mild
	13	Myalgia	17-APR-18	Possibly	Expected	2=Moderate
	14	Sore throat	24-DEC-17	Unlikely	Unexpected	1=Mild
	15	Pruritus	17-APR-18	Possibly	Expected	2=Moderate
	N	15	15	15	15	15
1019	1	Epididymitis	28-APR-18	Unlikely	Unexpected	2=Moderate
	2	Gastroenteritis	20-JUL-18	Possibly	Expected	1=Mild
	3	Common Cold	01-AUG-17	Unlikely	Expected	1=Mild
	4	Common Cold	23-NOV-17	Unlikely	Unexpected	2=Moderate
	N	4	4	4	4	4
1020	1	Pain in eyes	03-AUG-18	Possibly	Unexpected	2=Moderate
	2	Constipation	01-NOV-17	Possibly	Expected	1=Mild
	3	Nausea	01-JAN-18	Possibly	Expected	1=Mild
	4	Cracked lips	01-MAY-18	Unlikely	Unexpected	1=Mild
	5	Sore throat	01-MAY-18	Unlikely	Unexpected	1=Mild
	6	Fatigue	01-NOV-17	Possibly	Expected	1=Mild
	7	Increased thirst	04-FEB-18	Unlikely	Unexpected	1=Mild
	8	Fall (Of Unknown Cause)	10-JUL-18	Unlikely	Unexpected	1=Mild
	9	Myalgia	01-NOV-17	Possibly	Expected	1=Mild
	10	Joint stiffness	20-SEP-18	Possibly	Expected	1=Mild
	11	Blurred vision	01-NOV-17	Unlikely	Expected	1=Mild
	12	Headache (Pins and needles in head)	03-JAN-18	Possibly	Expected	1=Mild
	13	Headache	05-FEB-18	Possibly	Expected	2=Moderate
	14	Headache	03-AUG-18	Possibly	Expected	2=Moderate
	15	Sleep Disturbance	03-AUG-18	Possibly	Expected	2=Moderate
	16	Common Cold	22-DEC-17	Unlikely	Unexpected	2=Moderate
	17	Cough	22-DEC-17	Unlikely	Unexpected	1=Mild
	18	nasopharyngitis	04-FEB-18	Possibly	Expected	2=Moderate
	19	pharyngolaryngeal pain	09-MAR-18	Possibly	Expected	2=Moderate
	N	19	19	19	19	19
1021	1	Dyspepsia	13-NOV-17	Possibly	Expected	1=Mild
	2	Exacerbation of dyspepsia	06-JUL-18	Possibly	Expected	2=Moderate
	3	Vivid dreams	13-NOV-17	Possibly	Expected	1=Mild
	4	Headache	03-DEC-17	Possibly	Expected	1=Mild
	5	Vivid dreams	07-MAR-18	Unlikely	Expected	1=Mild
	6	Vivid dreams	05-MAY-18	Possibly	Expected	2=Moderate
	7	Vivid dreams	05-JUL-18	Possibly	Expected	2=Moderate

	8	Vivid dreams	05-AUG-18	Possibly	Expected	2=Moderate
	9	Sleep disturbance	13-NOV-17	Possibly	Expected	1=Mild
	10	Sleep disturbance	07-MAR-18	Unlikely	Expected	1=Mild
	11	Sleep disturbance	05-MAY-18	Possibly	Expected	2=Moderate
	12	Sleep disturbance	12-OCT-18	Possibly	Expected	2=Moderate
	13	Vivid dreams	12-OCT-18	Possibly	Expected	2=Moderate
	14	Sleep disturbance	05-AUG-18	Possibly	Expected	2=Moderate
	15	Pruritis	05-MAY-18	Possibly	Expected	2=Moderate
	16	Hematospermia	23-NOV-17	Unlikely	Unexpected	1=Mild
	N	16	16	16	16	16
1022	1	Fatigue	04-MAY-18	Unlikely	Expected	2=Moderate
	2	Low Testosterone	04-JUN-18	Unlikely	Unexpected	2=Moderate
	3	Bone Ache	04-MAY-18	Unlikely	Unexpected	2=Moderate
	4	Neck stiffness	04-MAY-18	Unlikely	Expected	2=Moderate
	5	Cognitive impairment	02-JAN-18	Unlikely	Unexpected	1=Mild
	6	Depression	04-MAY-18	Unlikely	Unexpected	2=Moderate
	7	Common Cold	15-MAR-18	Unlikely	Expected	2=Moderate
	N	7	7	7	7	7
1023	1	?Infection of unknown cause	01-NOV-18	Unlikely	Unexpected	1=Mild
	2	Elevated serum Iron level	01-MAY-18	Unlikely	Unexpected	1=Mild
	3	Folate deficiency	01-NOV-18	Unlikely	Unexpected	1=Mild
	4	Arthritis (Hips)	28-MAR-18	Unlikely	Expected	1=Mild
	5	Myalgia (legs)	12-MAR-18	Possibly	Expected	1=Mild
	6	Cramps (legs)	12-MAR-18	Possibly	Expected	1=Mild
	7	Cramps in leg	06-JUL-18	Possibly	Expected	1=Mild
	8	Cramps	08-SEP-18	Possibly	Expected	2=Moderate
	9	Myalgia	18-APR-18	Possibly	Expected	2=Moderate
	10	Myalgia	16-OCT-18	Possibly	Expected	2=Moderate
	11	Vivid dreams	14-FEB-18	Possibly	Expected	1=Mild
	12	Vivid dreams	01-DEC-18	Possibly	Expected	1=Mild
	13	Common Cold	06-SEP-18	Unlikely	Unexpected	1=Mild
	14	Pruritis	14-FEB-18	Possibly	Expected	2=Moderate
	N	14	14	14	14	14
1024	1	Fatigue	01-MAR-18	Possibly	Expected	1=Mild
	2	'Lump' in knee	26-MAR-18	Unlikely	Unexpected	1=Mild
	3	Fatigue	20-JUL-18	Possibly	Expected	2=Moderate
	4	Fatigue	04-SEP-18	Possibly	Expected	2=Moderate
	5	Fatigue	18-DEC-18	Possibly	Expected	2=Moderate

	6	Pain in extremity (shin bone pain)	07-MAR-18	Possibly	Expected	1=Mild
	7	Myalgia	20-JUL-18	Possibly	Expected	2=Moderate
	8	Exacerbation of arthritis	01-JUL-18	Unlikely	Unexpected	1=Mild
	9	Myalgia (Limbs)	04-SEP-18	Possibly	Expected	2=Moderate
	10	Myalgia	22-NOV-18	Possibly	Expected	2=Moderate
	11	'Achy bones'	22-NOV-18	Possibly	Expected	2=Moderate
	12	Arthralgia	18-DEC-18	Possibly	Expected	2=Moderate
	13	Myalgia	18-DEC-18	Possibly	Expected	2=Moderate
	14	'Aching bones'	18-DEC-18	Possibly	Expected	2=Moderate
	15	Low mood	01-JAN-18	Unlikely	Unexpected	1=Mild
	16	'Tearfulness'	20-JUL-18	Possibly	Expected	2=Moderate
	N	16	16	16	16	16
1025	1	Sty on eyelid	28-APR-18	Unlikely	Unexpected	1=Mild
	2	'Flu-like' symptoms	23-AUG-18	Possibly	Unexpected	1=Mild
	3	Compressed nerve	15-DEC-18	Unlikely	Unexpected	1=Mild
	4	'Bone ache' in elbows	15-AUG-18	Possibly	Expected	1=Mild
	5	Common cold	15-FEB-18	Unlikely	Unexpected	2=Moderate
	6	Common cold	24-OCT-18	Unlikely	Unexpected	2=Moderate
	7	Rash	30-AUG-18	Unlikely	Expected	1=Mild
	8	Dizziness	27-JAN-19	Unlikely	Unexpected	2=Moderate
	N	8	8	8	8	8
1026	1	'Sensation of pulse in eyes and cheeks'	08-JAN-19	Possibly	Unexpected	2=Moderate
	2	Plantar fasciitis	02-MAY-18	Unlikely	Unexpected	2=Moderate
	3	Exacerbation of Myalgia	13-AUG-18	Possibly	Expected	2=Moderate
	4	Myalgia (chest, shoulders, feet)	08-JAN-19	Possibly	Expected	2=Moderate
	5	'Influenza'	07-FEB-19	Unlikely	Unexpected	2=Moderate
	N	5	5	5	5	5
1027	1	Bloatedness	01-AUG-18	Possibly	Expected	1=Mild
	2	diarrhoea	01-JUL-18	Possibly	Expected	1=Mild
	3	Diarrhoea (After waking)	01-OCT-18	Possibly	Expected	1=Mild
	4	Influenza	16-FEB-19	Not related	Unexpected	3=Severe
	5	Strained Achilles tendon	17-AUG-18	Unlikely	Unexpected	2=Moderate
	6	Osteoarthritis (Left Arm)	29-APR-19	Not related	Unexpected	1=Mild

	7	Post-concussion syndrome (After large apple fell on head)	18-SEP-19	Not related	Unexpected	2=Moderate
	8	Abnormal right tonsil on imaging	22-AUG-19	Unlikely	Unexpected	2=Moderate
	9	Elective tonsillectomy	22-AUG-19	Not related	Expected	3=Severe
	N	9	9	9	9	9
1028	1	Fatigue	17-OCT-18	Possibly	Expected	2=Moderate
	2	Exacerbation of myalgia	17-OCT-18	Possibly	Expected	2=Moderate
	3	Muscle weakness	01-DEC-18	Possibly	Expected	2=Moderate
	4	'Achy Knees and feet'	18-MAY-18	Possibly	Expected	2=Moderate
	N	4	4	4	4	4
1029	1	Dizziness	26-APR-19	Possibly	Expected	2=Moderate
	2	Palpitations	26-APR-19	Possibly	Unexpected	2=Moderate
	3	Swollen Tongue	01-SEP-18	Unlikely	Unexpected	1=Mild
	4	Sore throat	01-SEP-18	Unlikely	Expected	1=Mild
	5	Increased bowel motions	01-SEP-18	Possibly	Expected	1=Mild
	6	'Dry Mouth'	26-APR-19	Possibly	Unexpected	2=Moderate
	7	Tiredness	01-SEP-18	Possibly	Expected	1=Mild
	8	Coldness of hands, feet, neck and mouth	12-DEC-18	Possibly	Unexpected	1=Mild
	9	'Mechanical' fall (tripped on step)	26-APR-19	Unlikely	Unexpected	1=Mild
	10	Myalgia	01-SEP-18	Possibly	Expected	1=Mild
	11	Myalgia	18-NOV-18	Possibly	Expected	1=Mild
	12	'Heaviness of limbs'	01-DEC-18	Possibly	Expected	2=Moderate
	13	Myalgia (arms, legs, back)	01-DEC-18	Possibly	Expected	2=Moderate
	14	Myalgia	01-MAR-19	Possibly	Expected	1=Mild
	15	Cramps	26-APR-19	Possibly	Expected	2=Moderate
	16	Increased urination	01-SEP-18	Possibly	Unexpected	1=Mild
	17	'Achy kidneys'	04-FEB-19	Unlikely	Unexpected	2=Moderate
	18	Skin Rash	15-DEC-18	Possibly	Expected	1=Mild
	19	Bruised hand and ankle	26-APR-19	Unlikely	Unexpected	2=Moderate
	N	19	19	19	19	19
1030	1	Fatigue	01-MAY-18	Possibly	Expected	2=Moderate
	2	'infected insect bite'	15-MAR-19	Unlikely	Unexpected	2=Moderate

	3	Jellyfish sting	15-JUN-18	Not related	Unexpected	2=Moderate
	4	Mechanical Fall "tripped in bathroom"	15-FEB-19	Unlikely	Unexpected	2=Moderate
	5	'Shin splints'	03-NOV-18	Possibly	Expected	2=Moderate
	6	Myalgia (shoulders)	10-DEC-18	Possibly	Expected	2=Moderate
	7	Myalgia (back)	09-DEC-18	Possibly	Expected	2=Moderate
	8	Myalgia in calves	01-MAY-18	Possibly	Expected	2=Moderate
	9	'Skinned toes'	15-FEB-19	Not related	Unexpected	1=Mild
	10	haematoma and bruising (chest)	15-FEB-19	Unlikely	Unexpected	2=Moderate
	N	10	10	10	10	10
1031	1	Myalgia (Side of thigh)	06-MAY-18	Possibly	Expected	1=Mild
	2	Myalgia (Side of thighs)	03-JUN-18	Possibly	Expected	1=Mild
	3	Myalgia (thighs)	01-FEB-19	Possibly	Expected	2=Moderate
	4	Exacerbation of hip pain	31-JUL-18	Possibly	Expected	2=Moderate
	5	Knee pain	01-JAN-19	Unlikely	Expected	2=Moderate
	N	5	5	5	5	5
1032	1	Exacerbation of chronic pain	11-JUN-18	Not related	Unexpected	3=Severe
	N	1	1	1	1	1
1033	1	Polycythaemia	30-JUL-18	Unlikely	Unexpected	3=Severe
	N	1	1	1	1	1
1034	1	Myalgia	13-SEP-18	Possibly	Expected	2=Moderate
	2	Myalgia	14-JUN-19	Possibly	Expected	2=Moderate
	N	2	2	2	2	2
1035	1	Triple vessel disease	07-MAY-19	Unlikely	Unexpected	2=Moderate
	2	Bloatedness	24-AUG-18	Possibly	Expected	1=Mild
	3	Cramps	31-AUG-18	Possibly	Expected	1=Mild
	4	Triple heart bypass	12-JUN-19	Unlikely	Unexpected	3=Severe
	5	Myocardial Infarction	04-MAY-19	Unlikely	Unexpected	4=Life threatening or disabling
	N	5	5	5	5	5
1036	1	'Food poisoning'	30-NOV-18	Unlikely	Unexpected	2=Moderate
	2	Worsening of gastro-intestinal reflux (at night)	07-MAR-19	Unlikely	Unexpected	2=Moderate
	3	Common Cold	01-DEC-18	Unlikely	Unexpected	2=Moderate
	4	Type 2 Diabetes 1	13-Mar-20	Not related	Expected	1=Mild
	N	4	4	4	4	4

1037	1	Fatigue	09-OCT-18	Possibly	Expected	2=Moderate
	2	Common cold	21-NOV-18	Not related	Unexpected	2=Moderate
	3	Myalgia	09-OCT-18	Possibly	Expected	2=Moderate
	4	'Irritable' mood	09-OCT-18	Possibly	Expected	2=Moderate
	N	4	4	4	4	4
1038	1	Exacerbation of cough	25-NOV-18	Unlikely	Expected	1=Mild
	2	Elective right shoulder hemiarthroplasty	24-SEP-19	Not related	Unexpected	3=Severe
	3	Iron deficiency	27-Jan-20	Not related	Unexpected	2=Moderate
	4	'Night sweats'	27-Sep-19	Not related	Unexpected	2=Moderate
	5	Weight loss	27-Sep-19	Unlikely	Expected	2=Moderate
	6	First stage of revision of right shoulder hemiarthroplasty	04-Feb-20	Not related	Unexpected	2=Moderate
	7	?septic right shoulder joint	04-Feb-20	Not related	Unexpected	2=Moderate
	8	Neutropenia	20-Feb-20	Not related	Unexpected	2=Moderate
	9	Hyponatraemia	20-Feb-20	Not related	Unexpected	2=Moderate
	10	Sepsis	20-Feb-20	Not related	Unexpected	4=Life threatening or disabling
	11	Bilateral pulmonary effusion with atelectasis	20-Feb-20	Not related	Unexpected	3=Severe
	N	11	11	11	11	11
1039	1	'Chest tightness'	29-AUG-19	Unlikely	Unexpected	1=Mild
	2	Palpitations	01-AUG-19	Unlikely	Unexpected	1=Mild
	3	Chest infection	01-FEB-19	Not related	Unexpected	2=Moderate
	4	Infection of gum	06-JUN-19	Unlikely	Unexpected	2=Moderate
	5	Dental abscess	01-OCT-19	Unlikely	Unexpected	2=Moderate
	6	Mechanical fall	01-FEB-19	Unlikely	Unexpected	1=Mild
	7	Fractured ribs	01-FEB-19	Not related	Expected	2=Moderate
	8	Ankle and shoulder swelling (following left shoulder replacement)	02-AUG-19	Unlikely	Unexpected	1=Mild
	9	'Erratic heart beat'	12-JUN-19	Unlikely	Unexpected	1=Mild
	10	Myalgia wrist	04-DEC-18	Possibly	Expected	1=Mild
	11	leg cramps	01-DEC-18	Possibly	Expected	1=Mild
	12	Cramps	01-JAN-19	Possibly	Expected	1=Mild

	13	Cramps (hands, forearms, calves)	09-JUN-19	Possibly	Expected	1=Mild
	14	Cramps	13-OCT-19	Possibly	Expected	1=Mild
	15	Right total shoulder replacement	13-MAR-19	Not related	Unexpected	2=Moderate
	16	Left Total Shoulder Replacement	26-JUL-19	Not related	Unexpected	2=Moderate
	17	Haematoma (following left shoulder replacement)	02-AUG-19	Unlikely	Unexpected	1=Mild
	N	17	17	17	17	17
1040	1	Fatigue	03-JAN-19	Possibly	Expected	2=Moderate
	2	Myalgia	03-JAN-19	Possibly	Expected	2=Moderate
	3	Arthralgia	03-JAN-19	Possibly	Expected	2=Moderate
	4	Myalgia	01-FEB-19	Possibly	Expected	2=Moderate
	5	Pruritus	03-JAN-19	Possibly	Expected	2=Moderate
	N	5	5	5	5	5
1041	1	Urinary urgency	06-DEC-18	Possibly	Expected	2=Moderate
	N	1	1	1	1	1
1042	1	'cold' sensation in toes	20-FEB-19	Not related	Unexpected	2=Moderate
	2	Common cold	20-FEB-19	Not related	Unexpected	2=Moderate
	3	'Mechanical' fall	18-FEB-19	Unlikely	Unexpected	2=Moderate
	4	Mechanical fall	01-JUN-19	Unlikely	Expected	2=Moderate
	5	Mechanical fall	20-MAY-19	Unlikely	Unexpected	2=Moderate
	6	Fractured finger	18-FEB-19	Not related	Unexpected	2=Moderate
	7	'Achy' feet	20-FEB-19	Possibly	Expected	2=Moderate
	8	Myalgia	06-JUN-19	Possibly	Expected	2=Moderate
	9	'Pain' in Achilles heel	01-JUN-19	Unlikely	Expected	2=Moderate
	10	Exacerbation of pain in thumbs (Related to excessive knitting)	01-SEP-19	Not related	Expected	2=Moderate
	11	Myalgia	05-MAY-19	Possibly	Expected	2=Moderate
	12	Depression	18-APR-19	Possibly	Expected	2=Moderate
	13	Low mood	06-JUN-19	Possibly	Expected	2=Moderate
	14	'breakable nails'	10-APR-19	Not related	Unexpected	2=Moderate
	15	'Bruised' hip, arms and ribs	18-FEB-19	Not related	Unexpected	2=Moderate
	N	15	15	15	15	15
1043	1	Lightheadness	07-OCT-19	Possibly	Expected	2=Moderate
	2	Fatigue	07-APR-19	Possibly	Expected	1=Mild

	3	Common cold	15-SEP-19	Unlikely	Expected	1=Mild
	4	Myalgia	07-APR-19	Possibly	Expected	1=Mild
	5	Myalgia	09-NOV-19	Possibly	Expected	2=Moderate
	6	Cramping	09-NOV-19	Possibly	Expected	2=Moderate
	7	Myalgia	08-DEC-19	Possibly	Expected	2=Moderate
	8	Pain in limbs	07-OCT-19	Possibly	Expected	2=Moderate
	9	Cramping	08-DEC-19	Possibly	Expected	2=Moderate
	10	'Reduced cognition'	07-APR-19	Possibly	Unexpected	1=Mild
	11	Tooth extraction	30-MAR-19	Not related	Unexpected	2=Moderate
	12	Myalgia	25-Aug-20	Not related	Expected	1=Mild
	N	12	12	12	12	12
1044	1	Chest infection	06-JAN-20	Unlikely	Unexpected	2=Moderate
	2	Common Cold	22-NOV-19	Unlikely	Expected	2=Moderate
	3	Heart rate increased	27-JAN-20	Unlikely	Unexpected	1=Mild
	4	'Torn muscle'	01-FEB-19	Unlikely	Unexpected	1=Mild
	5	Myalgia	01-NOV-19	Possibly	Expected	1=Mild
	6	Cough	22-NOV-19	Unlikely	Unexpected	2=Moderate
	7	Endoscopic resection of prostate (TURP) (including cystoscopy)	27-JAN-20	Not related	Unexpected	2=Moderate
	N	7	7	7	7	7
1045	1	Fatigue	01-OCT-19	Possibly	Expected	1=Mild
	2	Muscle weakness	05-OCT-19	Possibly	Expected	1=Mild
	3	Myalgia	05-AUG-19	Possibly	Expected	1=Mild
	4	'hot' sweats	01-MAR-19	Unlikely	Unexpected	2=Moderate
	5	Grade II invasive ductal carcinoma of left breast	13-Aug-20	Not related	Unexpected	4=Life threatening or disabling
	N	5	5	5	5	5
1046	1	Fatigue	11-JAN-20	Possibly	Expected	1=Mild
	2	Fatigue	24-JUN-19	Possibly	Expected	2=Moderate
	3	'Flu like symptoms'	08-APR-19	Possibly	Expected	2=Moderate
	4	'Flu-like symptoms'	24-JUN-19	Possibly	Unexpected	2=Moderate
	5	Fatigue	11-JUL-19	Possibly	Expected	2=Moderate
	6	Fatigue	06-DEC-19	Possibly	Expected	2=Moderate
	7	Fatigue	08-APR-19	Possibly	Expected	2=Moderate
	8	Myalgia	18-MAR-19	Possibly	Expected	2=Moderate
	9	myalgia	08-APR-19	Possibly	Expected	2=Moderate
	10	Myalgia	11-JUL-19	Possibly	Expected	2=Moderate
	11	Arthralgia	06-DEC-19	Possibly	Expected	2=Moderate

	12	Myalgia	11-JAN-20	Possibly	Expected	1=Mild
	13	Arthralgia	11-JAN-20	Possibly	Expected	1=Mild
	14	Headache	18-MAR-19	Possibly	Expected	2=Moderate
	15	'Low mood'	11-JUL-19	Possibly	Expected	2=Moderate
	16	Cough	17-MAY-19	Unlikely	Unexpected	1=Mild
	17	Acute nasopharyngitis	17-MAY-19	Unlikely	Unexpected	1=Mild
	18	Cough	11-NOV-19	Unlikely	Unexpected	2=Moderate
	N	18	18	18	18	18
1047	1	'Racing heart'	04-APR-19	Possibly	Unexpected	1=Mild
	2	Abdominal pain	01-JUN-19	Unlikely	Expected	1=Mild
	3	Fatigue	01-JUN-19	Possibly	Expected	1=Mild
	4	Malaise	04-APR-19	Possibly	Expected	1=Mild
	5	Fatigue	04-APR-19	Possibly	Expected	1=Mild
	6	Exacerbation General malaise	01-AUG-19	Possibly	Expected	2=Moderate
	7	Heart rate increased	03-JAN-20	Unlikely	Unexpected	1=Mild
	8	myalgia	02-FEB-19	Possibly	Expected	2=Moderate
	9	Arthralgia	02-FEB-19	Possibly	Expected	2=Moderate
	10	Arthralgia	04-JUL-19	Possibly	Expected	1=Mild
	11	Muscle weakness	04-APR-19	Possibly	Expected	2=Moderate
	12	Myalgia	04-APR-19	Possibly	Expected	1=Mild
	13	Exacerbation of myalgia	01-AUG-19	Possibly	Expected	2=Moderate
	14	Exacerbation of arthralgia	01-AUG-19	Possibly	Expected	2=Moderate
	15	Exacerbation muscle weakness	01-AUG-19	Possibly	Expected	2=Moderate
	16	Trembling	04-APR-19	Possibly	Expected	1=Mild
	17	'Forgetfulness'	30-AUG-19	Possibly	Expected	2=Moderate
	18	Pruritus	01-AUG-19	Possibly	Expected	2=Moderate
	19	Alopecia	15-JAN-20	Possibly	Expected	1=Mild
	20	Seborrheic dermatitis (Scalp)	15-JAN-20	Unlikely	Expected	2=Moderate
	21	Arrythmia	30-Apr-20	Not related	Unexpected	2=Moderate
	N	21	21	21	21	21
1048	1	'Pre-diabetes' HbA1c 43mmol/l	23-MAY-19	Possibly	Expected	1=Mild
	2	?Food poisoning	25-JUL-19	Unlikely	Unexpected	1=Mild
	3	Vomiting	25-JUL-19	Unlikely	Expected	1=Mild
	4	Flu-like symptoms	20-JUN-19	Unlikely	Unexpected	1=Mild
	5	'Flu-like' symptoms	25-OCT-19	Unlikely	Unexpected	2=Moderate

	6	Myalgia	01-MAY-19	Possibly	Expected	1=Mild
	7	'Trigger finger' of left little finger	07-SEP-19	Unlikely	Expected	2=Moderate
	8	Agitation	14-DEC-19	Possibly	Unexpected	1=Mild
	9	Sleep disruption	04-FEB-19	Possibly	Expected	2=Moderate
	10	Memory loss	22-FEB-19	Possibly	Expected	1=Mild
	11	Irritability	22-FEB-19	Possibly	Unexpected	2=Moderate
	12	Productive cough	25-OCT-19	Unlikely	Unexpected	2=Moderate
	13	Skin rash (Red and white spots around neck)	14-DEC-19	Unlikely	Expected	1=Mild
	14	Globus feeling in pharynx	01-Mar-20	Unlikely	Unexpected	2=Moderate
	N	14	14	14	14	14
1049	1	'Tooth pain'	10-APR-19	Not related	Unexpected	2=Moderate
	2	Gastrointestinal disturbance	26-FEB-19	Possibly	Expected	2=Moderate
	3	Excessive saliva production	01-APR-19	Unlikely	Unexpected	2=Moderate
	4	'Discomfort' in stomach	01-SEP-19	Unlikely	Expected	2=Moderate
	5	Dental infection	01-APR-19	Unlikely	Unexpected	2=Moderate
	6	Left Bursitis of knee	15-MAY-19	Unlikely	Unexpected	2=Moderate
	7	Lower back ache	14-FEB-19	Possibly	Expected	2=Moderate
	8	Lower back ache	26-FEB-19	Unlikely	Expected	2=Moderate
	9	Lower back ache	02-SEP-19	Possibly	Expected	2=Moderate
	10	Lower back ache	18-OCT-19	Possibly	Expected	2=Moderate
	11	Lower back ache	14-DEC-19	Possibly	Expected	2=Moderate
	12	Low mood	01-NOV-19	Unlikely	Expected	1=Mild
	13	'Runny nose'	26-FEB-19	Possibly	Unexpected	2=Moderate
	14	Nasal congestion	25-DEC-19	Unlikely	Expected	2=Moderate
	15	Rectal Bleeding	22-Aug-20	Not related	Unexpected	2=Moderate
	N	15	15	15	15	15
1050	1	Common cold	08-NOV-19	Unlikely	Expected	1=Mild
	2	Common cold	25-DEC-19	Unlikely	Expected	1=Mild
	3	Myalgia (hands)	01-MAY-19	Possibly	Expected	1=Mild
	4	Myalgia (wrists)	01-JUL-19	Possibly	Expected	1=Mild
	5	Myalgia	01-APR-19	Possibly	Expected	1=Mild
	6	Myalgia (between thumb and wrist)	15-SEP-19	Possibly	Expected	1=Mild
	7	Arthralgia (thumb joints)	01-DEC-19	Possibly	Expected	1=Mild
	8	Urinary tract infection	22-MAR-19	Unlikely	Unexpected	2=Moderate

	9	Urinary tract infection	31-MAY-19	Not related	Unexpected	2=Moderate
	10	Finger laceration	23-DEC-19	Not related	Unexpected	1=Mild
	11	Shortness of breath	10-Jun-20	Not related	Unexpected	2=Moderate
	N	11	11	11	11	11
1051	1	Gastroenteritis	14-JAN-20	Unlikely	Expected	2=Moderate
	2	Cramps	03-SEP-19	Possibly	Expected	1=Mild
	3	'Stiff' legs	04-DEC-19	Possibly	Expected	1=Mild
	4	Joint pain (legs)	15-FEB-20	Possibly	Expected	1=Mild
	5	Arthralgia	15-FEB-20	Possibly	Expected	1=Mild
	6	Low mood	01-JUN-19	Unlikely	Expected	1=Mild
	7	Cataract removal (both eyes)	30-AUG-19	Not related	Unexpected	2=Moderate
	8	Circumcision (Lichen Sclerosis)	04-NOV-19	Not related	Unexpected	2=Moderate
	9	Anxiety	16-Mar-20	Not related	Unexpected	1=Mild
	10	Cramping (right leg)	09-Jun-20	Not related	Expected	2=Moderate
	11	Joint pain	09-Jun-20	Not related	Expected	2=Moderate
	N	11	11	11	11	11
1052	1	'Pounding heart'	20-MAY-19	Unlikely	Expected	2=Moderate
	2	Blocked left tear duct	14-AUG-19	Unlikely	Unexpected	1=Mild
	3	Nausea	20-MAY-19	Possibly	Expected	1=Mild
	4	Retching	20-MAY-19	Unlikely	Expected	2=Moderate
	5	Weight loss	20-MAY-19	Unlikely	Expected	2=Moderate
	6	Hip pain	08-NOV-19	Possibly	Expected	1=Mild
	7	Sleep disturbance	07-MAR-19	Possibly	Expected	2=Moderate
	8	Anxiety	01-MAY-19	Unlikely	Unexpected	2=Moderate
	9	Cough	09-NOV-19	Unlikely	Unexpected	1=Mild
	10	'Patchy' small vessel ischaemia in brain 'prominent for age' on MRI scan	14-Sep-20	Not related	Unexpected	2=Moderate
	N	10	10	10	10	10
1053	1	Lightheadness	25-MAR-19	Not related	Unexpected	1=Mild
	2	Fatigue	25-MAR-19	Not related	Unexpected	1=Mild
	3	Common cold	15-OCT-19	Unlikely	Expected	1=Mild
	4	Cough	10-DEC-19	Unlikely	Unexpected	2=Moderate
	N	4	4	4	4	4
1054	1	Pain in chest of unknown origin	08-MAR-19	Possibly	Expected	2=Moderate

	2	Constipation	23-MAY-19	Unlikely	Expected	2=Moderate
	3	'Tightness in chest'	08-MAR-19	Possibly	Unexpected	2=Moderate
	4	Chest pain (of unknown cause)	12-JUN-19	Unlikely	Expected	1=Mild
	5	Leg pains	02-AUG-19	Possibly	Expected	2=Moderate
	6	Myalgia	02-OCT-19	Possibly	Expected	2=Moderate
	7	Breathlessness	12-JUN-19	Unlikely	Unexpected	2=Moderate
	8	Breathlessness	06-AUG-19	Possibly	Unexpected	2=Moderate
	N	8	8	8	8	8
1055	1	Common cold	15-MAY-19	Unlikely	Unexpected	1=Mild
	2	Common cold	24-DEC-19	Unlikely	Expected	1=Mild
	3	Worsening gout	30-AUG-19	Unlikely	Unexpected	1=Mild
	4	Arthralgia	21-OCT-19	Possibly	Expected	1=Mild
	5	'strained' shoulder and neck	04-FEB-20	Unlikely	Expected	2=Moderate
	6	Headache	15-APR-19	Possibly	Expected	2=Moderate
	7	Urinary urgency	15-APR-19	Not related	Unexpected	2=Moderate
	8	Urinary incontinence	15-APR-19	Not related	Expected	2=Moderate
	9	Common cold	07-NOV-19	Unlikely	Expected	1=Mild
	10	Knuckle pain	01-Jun-20	Not related	Expected	1=Mild
	N	10	10	10	10	10
1056	1	Ectopic heartbeats	24-JUN-19	Unlikely	Unexpected	2=Moderate
	2	'Dislodged floater' in eye	11-SEP-19	Unlikely	Unexpected	1=Mild
	3	Laceration of cornea (on twig)	24-FEB-20	Unlikely	Unexpected	2=Moderate
	4	Exacerbation of hiatus hernia	02-APR-19	Not related	Unexpected	2=Moderate
	5	Fatigue	05-APR-19	Possibly	Expected	2=Moderate
	6	Mammogram normal	20-JAN-20	Not related	Unexpected	1=Mild
	7	Reduced cognitive function	04-APR-19	Possibly	Unexpected	1=Mild
	8	Reduced cognitive function	02-JUN-19	Possibly	Unexpected	2=Moderate
	9	Reduced cognitive function	03-SEP-19	Possibly	Expected	2=Moderate
	10	Reduced cognition 'fuzzy head'	09-DEC-19	Possibly	Unexpected	2=Moderate

	11	Reduced cognitive function	01-FEB-20	Possibly	Unexpected	2=Moderate
	12	Left Breast tenderness	01-NOV-19	Not related	Unexpected	2=Moderate
	13	Exacerbation of hiatus hernia	26-FEB-20	Unlikely	Unexpected	2=Moderate
	14	Migraines	01-NOV-19	Unlikely	Expected	1=Mild
	15	Arthralgia	01-Apr-20	Not related	Expected	2=Moderate
	N	15	15	15	15	15
1057	1	Palpitations	20-APR-19	Unlikely	Unexpected	1=Mild
	2	Constipation	03-MAY-19	Unlikely	Expected	1=Mild
	3	Constipation	04-AUG-19	Possibly	Expected	1=Mild
	4	Constipation	23-OCT-19	Possibly	Expected	1=Mild
	5	Indigestion	15-NOV-19	Unlikely	Expected	2=Moderate
	6	Bloating	03-MAR-20	Unlikely	Expected	1=Mild
	7	Lethargy	09-MAY-19	Unlikely	Expected	1=Mild
	8	Common cold	08-APR-19	Not related	Expected	1=Mild
	9	Common cold	15-MAY-19	Unlikely	Expected	1=Mild
	10	Viral infection	23-JAN-20	Unlikely	Expected	2=Moderate
	11	Sleep disturbance	07-MAY-19	Unlikely	Expected	1=Mild
	12	Sleep disturbance	16-AUG-19	Possibly	Expected	1=Mild
	13	Sleep disturbance	23-OCT-19	Possibly	Expected	1=Mild
	14	Insomnia	23-JAN-20	Possibly	Expected	1=Mild
	15	Nightmares	23-JAN-20	Possibly	Expected	1=Mild
	16	Hiatus Hernia	03-MAR-20	Unlikely	Unexpected	2=Moderate
	17	Post-operative haemoperitoneum	19-May-20	Not related	Unexpected	3=Severe
	18	Ovarian cyst	03-Apr-20	Not related	Unexpected	3=Severe
	19	Bilateral Salpingo-Oophorectomy	19-May-20	Not related	Unexpected	3=Severe
	N	19	19	19	19	19
1058	1	Palpitations	11-OCT-19	Unlikely	Unexpected	1=Mild
	2	Right ankle oedema	29-FEB-20	Unlikely	Expected	1=Mild
	3	Dry eyes	14-AUG-19	Possibly	Unexpected	1=Mild
	4	'Loose bowels'	12-APR-19	Possibly	Expected	1=Mild
	5	Fatigue	12-APR-19	Possibly	Expected	1=Mild
	6	Chest Pain at rest (of unknown cause)	06-JUN-19	Unlikely	Expected	1=Mild
	7	Dull ache in chest	03-NOV-19	Unlikely	Expected	2=Moderate

	8	Common cold	01-DEC-19	Not related	Unexpected	1=Mild
	9	Common cold	01-JAN-20	Unlikely	Expected	1=Mild
	10	Myalgia (back and calves)	16-APR-19	Possibly	Expected	1=Mild
	11	Cramp	05-JUL-19	Possibly	Expected	1=Mild
	12	Muscular stiffness	14-AUG-19	Possibly	Expected	1=Mild
	13	Arthralgia	01-DEC-19	Possibly	Expected	1=Mild
	14	Cramping in right leg	29-FEB-20	Possibly	Expected	1=Mild
	15	Sleep disturbance	18-MAR-19	Possibly	Expected	2=Moderate
	16	Exacerbation of sleep disturbance	14-AUG-19	Possibly	Expected	2=Moderate
	17	Chest pain (of unknown cause)	11-OCT-19	Unlikely	Expected	1=Mild
	18	nasopharyngitis (sneezing and runny nose)	01-JUL-19	Unlikely	Expected	1=Mild
	19	Common cold	15-JAN-20	Unlikely	Expected	1=Mild
	20	Coronary artery spasm	25-OCT-19	Unlikely	Unexpected	2=Moderate
	N	20	20	20	20	20
1059	1	Damaged ligament and tendons (Right knee- Sport related injury)	01-SEP-19	Unlikely	Expected	2=Moderate
	2	Mild myalgia	01-JUL-19	Possibly	Expected	1=Mild
	3	Pain in hands and wrists	06-SEP-19	Possibly	Expected	2=Moderate
	4	Osteoarthritis	15-JAN-20	Unlikely	Unexpected	1=Mild
	5	Pain in hands and feet	26-OCT-19	Possibly	Expected	2=Moderate
	6	Myalgia in hand and feet	06-DEC-19	Possibly	Expected	2=Moderate
	7	Type A influenza	30-MAR-19	Not related	Unexpected	3=Severe
	N	7	7	7	7	7
1060	1	Common cold	25-SEP-19	Unlikely	Expected	1=Mild
	2	Mechanical fall	09-OCT-19	Not related	Unexpected	1=Mild
	3	Exacerbation of knee 'pain'	18-MAR-19	Possibly	Expected	2=Moderate
	4	Exacerbation of knee pain	13-JUN-19	Possibly	Expected	1=Mild
	5	Abdominal pain	31-Jul-20	Not related	Expected	3=Severe
	N	4	4	4	4	4
1061	1	Dizziness	29-MAR-19	Possibly	Expected	2=Moderate

	2	Dizziness	01-JUL-19	Unlikely	Expected	2=Moderate
	3	Fatigue	03-SEP-19	Possibly	Expected	2=Moderate
	4	Common cold	02-JAN-20	Unlikely	Expected	1=Mild
	5	Fall from motorbike	19-AUG-19	Not related	Expected	1=Mild
	6	Fall (from motorbike)	09-MAR-20	Unlikely	Unexpected	1=Mild
	7	'Erratic heart beat'	29-MAR-19	Unlikely	Expected	2=Moderate
	8	'Pelvic Bone' Pain	26-APR-19	Unlikely	Expected	2=Moderate
	9	Myalgia	12-MAY-19	Possibly	Expected	2=Moderate
	10	Cramps (feet and legs)	01-JUL-19	Possibly	Expected	2=Moderate
	11	'tightness in calves'	01-JUL-19	Possibly	Expected	1=Mild
	12	Myalgia	01-JAN-20	Possibly	Expected	2=Moderate
	13	Cramps in legs (at night)	01-JAN-20	Possibly	Expected	1=Mild
	N	13	13	13	13	13
1062	1	Exacerbation of irritable bowel syndrome	22-MAR-19	Not related	Unexpected	2=Moderate
	2	'Flare-up of irritable bowel'	08-JAN-20	Unlikely	Unexpected	1=Mild
	3	Malaise	02-MAR-19	Possibly	Expected	2=Moderate
	4	Common cold	25-JUL-19	Unlikely	Expected	1=Mild
	5	Knee injury	20-FEB-20	Not related	Unexpected	1=Mild
	6	Myalgia (Calves)	02-APR-19	Possibly	Expected	2=Moderate
	7	Arthritis flare-up	12-JUL-19	Unlikely	Unexpected	2=Moderate
	8	myalgia in calves	15-OCT-19	Possibly	Expected	2=Moderate
	9	Removal of infected and impacted wisdom tooth	22-MAY-19	Not related	Expected	1=Mild
	10	Abdominal pain	31-Jul-20	Not related	Expected	3=Severe
	11	Intrahepatic cholangiocarcinoma	01-Sep-20	Not related	Unexpected	4=Life threatening or disabling
	12	Right hemihepatectomy	02-Sep-20	Not related	Unexpected	3=Severe
	13	Cholecystectomy	02-Sep-20	Not related	Unexpected	3=Severe
	14	Type 2 Diabetes Mellitus	16-Sep-20	Not related	Expected	1=Mild
	N	14	14	14	14	14
N	600		600	600	600	600

Appendix 21: Pilot study/interview study information sheets and consent forms

Imperial College London,
Peart-Rose Research Unit,
1st Floor, Block C,
Hammersmith Hospital,
Du Cane Road,
London
W12 0HS

P: 0207 594 9647
F:0203 3137348
E: frances.wood@imperial.nhs.uk

Dear Sir/ Madam,

Participant Information Leaflet

Pilot Study

Self Assessment Method for Statin side-effects Or Nocebo (SAMSON)

We invite you to consider taking part in a pilot research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

Why have I been chosen?
You are being invited to participate in an interview about your current or past use of statin medication.

Background
High cholesterol is a major risk factor for cardiovascular disease. Statins lower cholesterol and many expert committees advise their use to prevent cardiovascular disease. Despite their beneficial effects, some people who are prescribed statins develop symptomatic side effects which lead them to stop taking their medication.

Evidence from over 80,000 trial participants, who were either taking a statin or a placebo (dummy drug) showed no tendency to experience more symptomatic side effects with statins than with a placebo. This indicates that adverse symptoms experienced on statins may not be solely due to the medication. This study will explore statin side effects to understand how they can best be assessed.

About this information sheet
Before you decide whether or not to participate in this study please read the following information sheet. If there is anything you do not understand or wish to know please ask the Study Team.

What is the aim of this study?
Our aim is to gain a better understanding of individual's experiences and side effects whilst taking statins. This information will be used to develop a self-assessment method for assessing statin side effects. This method will then be tested in further research.

What are the possible benefits of taking part?
There are unlikely to be any direct benefits for you. Your involvement will help explore important questions about side effects that cause people to stop taking statins. The results may improve the care of future patients.

What would participation involve?
You will be interviewed by a research nurse. The interview will last no longer than an hour and a half. We will record the interview so that we can review your responses. This recording will not include personal information that could identify you. The recording will be kept until the end of the study at which point it will be destroyed.

The interview will be in two parts. Firstly, the research nurse will ask questions about your previous experience of taking statins. Secondly, the nurse will ask you to complete two health questionnaires. We will ask you to give us feedback about these questionnaires.

Do I have to take part?
Your participation is voluntary. If you decide not to take part, this will not affect the care that you normally receive. If you do decide to take part, you are free to withdraw at any time without giving a reason.

What are the risks of taking part?
There is a risk that you might find the interview upsetting. If this happens, we will stop immediately. We will only start again if you agree.

Cost and reimbursement?
Your travel expenses will be reimbursed.

What if something goes wrong?
We do not anticipate that you will come to any harm and we will be attentive to your wellbeing. However, should any problem arise we will review this carefully and take appropriate action.

Imperial College London holds insurance policies which apply to this study. If you experience serious injury as a result of taking part in this study, you may be eligible for compensation without having to prove that the College is at fault. This does not affect your legal rights to compensation. If you wish to complain, or have any concerns about

any aspect of the way you have been treated during the course of this study then you should inform the Investigator (contact details given below). The normal National Health Service complaint complaints mechanisms are also available to you on 030 0330 5454. If you are still not satisfied with the response, you may contact the Imperial AHSC Joint Research Office.

What if relevant new information becomes available?

Sometimes during the course of research, new information becomes available about the issues being studied which could influence participants' willingness to participate. Although unlikely in this project, if this happens, your research nurse will tell you.

Will my taking part in this study be kept confidential?

If you agree to take part in this study, your identity will be known only to the researchers and referenced by an anonymous study number. Your details, the interview recordings and information relevant to the study will be held on a password-protected computer. Any paper records will be kept in locked offices within the research facility accessible only to the research team, the sponsor and regulatory authorities. We will contact your GP to inform them you are participating and will provide them with information regarding the study. The handling, processing, storage and eventual destruction of your data will be compliant with the Data Protection Act 1998.

What will happen to the results of the research study?

Results from this research may be presented at medical meetings and published, but your participation in the study will not be made known. We will send you a summary of the findings and its implications.

Who is organising and funding the research?

This project has been organised by Imperial College London. This research is funded by the British Heart Foundation.

Who has reviewed the study?

This project has been reviewed by London Brent Research Ethics Committee, REC reference: 15/LO/1761.

Contact details for further information

Now or during the course of the study, if you have any needs or questions concerning this study or your rights as a participant, you should contact your study doctor Prof Darrel Francis, or nurse Frances Wood on 0207 594 9647. Or for independent advice, please contact the NHS patient advisory liaison service (PALS) 020 313 0088.

Thank you for taking the time to consider participating in this study. A copy of this information sheet and of the consent form will be given to you.

Imperial College London | Imperial College Healthcare NHS Trust | SAMSON Self-Assessment Method for Statin side effects Or Nocebo | British Heart Foundation

CONSENT FORM

Pilot Study

Self Assessment Method for Statin side-effects Or Nocebo (SAMSON)

Chief and Principal Investigator: Professor Darrel Francis
Imperial College London, Peart-Rose Research Unit, 1st Floor, Block C, Hammersmith Hospital, Du Cane Road, London, W12 0HS

Please read each statement	*Please initial as applicable*
I have read the Patient Information Sheet Version 1.0 (Dated: 20/10/2014).	Yes …… No……
I have received enough information about this study, had the opportunity to ask questions and I am satisfied with the answers to my questions.	Yes …… No……
I understand that I am free to withdraw from the study at any time without giving a reason and without affecting my future care or legal rights.	Yes …… No……
I understand that my voice will be recorded during the interview and that a written transcript will be made of what I have said.	Yes …… No……
I understand that these voice recordings will be kept until the end of the study at which point they will be destroyed.	Yes …… No……
I agree to be contacted by the researcher by telephone for follow up questions if necessary.	Yes …… No……
I am willing for my anonymous research data, and the results arising from the study, to be used as appropriate.	Yes …… No……
I understand that relevant sections of my medical notes and data collected during the study may be looked at by responsible individuals from Imperial College, from regulatory authorities or from the Imperial Healthcare NHS Trust. I give permission for these individuals to access my records.	Yes …… No……
I agree for my contact details to be kept on record for future research studies at Imperial College London.	Yes …… No……
I understand that a product(s) may be developed through the use of my medical information collected during this study but neither Imperial College London nor the researchers will compensate me if this happens and I do not have any rights to future inventions. I give my permission for the processing of my information.	Yes …… No……
I agree to my GP being informed about my participation in this research study.	Yes …… No……
I agree to take part in this research study.	Yes …… No……

Signature of research participant .....……

Name of research participant (block capitals) .....……..
Date…….

Signature of study investigator .....

Name of Study Investigator (block capitals).....…….
Date……..

Imperial College London

Imperial College Healthcare NHS Trust

SAMSON
Self-Assessment Method for Statin side effects Or Nocebo

British Heart Foundation

CONSENT FORM

Pilot Study

Self Assessment Method for Statin side-effects Or Nocebo (SAMSON)

Chief and Principal Investigator: Professor Darrel Francis
Imperial College London, Peart-Rose Research Unit, 1st Floor, Block C, Hammersmith Hospital, Du Cane Road, London, W12 0HS

Please read each statement out to the participant	*Researcher initial as applicable*
I have read the Patient Information Sheet Version 1.0 (Dated: 20/10/2014).	Yes …… No……
I have received enough information about this study, had the opportunity to ask questions and I am satisfied with the answers to my questions.	Yes …… No……
I understand that I am free to withdraw from the study at any time without giving a reason and without affecting my future care or legal rights.	Yes …… No……
I understand that my voice will be recorded during the interview and that a written transcript will be made of what I have said.	Yes …… No……
I understand that these voice recordings will be kept until the end of the study at which point they will be destroyed.	Yes …… No……
I agree to be contacted by the researcher by telephone for follow up questions if necessary.	Yes …… No……
I am willing for my anonymous research data, and the results arising from the study, to be used as appropriate.	Yes …… No……
I understand that relevant sections of my medical notes and data collected during the study may be looked at by responsible individuals from Imperial College, from regulatory authorities or from the Imperial Healthcare NHS Trust. I give permission for these individuals to access my records.	Yes …… No……
I agree for my contact details to be kept on record for future research studies at Imperial College London.	Yes …… No……
I understand that a product(s) may be developed through the use of my medical information collected during this study but neither Imperial College London nor the researchers will compensate me if this happens and I do not have any rights to future inventions. I give my permission for the processing of my information.	Yes …… No……
I agree to my GP being informed about my participation in this research study.	Yes …… No……
I agree to take part in this research study.	Yes …… No……

Verbal consent of participant Yes ☐ No☐

Name of research participant (block capitals) .....……..
Date…….

Signature of study investigator .....

Name of Study Investigator (block capitals).....…….
Date……..

Appendix 22: Topic guide for qualitative interviews

Questions:

- Have you ever been or are you currently taking statins?
- Can you tell me a bit about your experience of taking statins?
- Can you tell me the reason you are taking or took statins?
- Can you tell me the reason you stopped/continue taking statins?
- Were there any good points or bad points about the statin you were taking?
- Have you even experienced a side effects on statins or any other medicine you have taken?

Appendix 23: SAMSON Trial article trending on BBC News