Gaps in patient reported outcome measures in randomised clinical trials of cardiac catheter ablation: a systematic review

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ABSTRACT

Aims

To systematically evaluate randomised clinical trials of cardiac catheter ablation and to assess the prevalence, characteristics and reporting standards of clinically relevant patient reported outcome measures (PROMs).

Methods and Results

Electronic database searches of Medline, Embase, CENTRAL and the WHO Trial Registry were conducted in March 2019. The study protocol was registered on PROSPERO (CRD42019133086). Of 7,125 records identified, 237 RCTs were included for analysis, representing 35,427 patients with a mean age of 59 years. Only 43 RCTs (18%) reported PROMs of which 27 included a generic PROM that measured health-related quality of life (HRQL) necessary to conduct comparative effectiveness research. There was notable under-representation of certain patient groups - only 31% were women and only 8% were of non-Caucasian ethnicity, in trials which reported such data. The reporting standard of PROMs was highly variable with 8-62% adherence against CONSORT PRO specific items.

Conclusion

PROMs play a crucial role in determining the clinical and cost effectiveness of treatments which primarily offer symptomatic improvement, such as cardiac catheter ablation (CCA). Their underuse significantly limits evaluation of the comparative effectiveness of treatments. Using CCA as an exemplar, there are additional issues of infrequent assessment, poor reporting and under-representation of many population groups. Greater use of PROMs, and specifically validated HRQL questionnaires, is paramount in giving patients a voice in studies, generating more meaningful comparisons between treatments and driving better patient-centred clinical and policy-level decision making.

Keywords

Patient Reported Outcome Measures (PROMs), Cardiac catheter ablation, Health related quality of life (HRQL), Cost-effectiveness

INTRODUCTION

Randomised clinical trials (RCTs) in cardiology have failed to adequately include patient-reported outcome measures (PROMs). A previous systematic review highlighted that only 16% of RCTs had PROMs.[1] Embedding PROMs in clinical studies is paramount to ensuring research aligns with patient-centred values and in 2014 the European Society of Cardiology proposed their mandatory integration into future RCTs.[2]

Cardiology uses a large and growing number of medical devices and interventions, including cardiac catheter ablation (CCA) as an established means to treat symptomatic arrhythmias.[3] An increasing number of patients are selected to undergo CCA. In the US, more than half a million ablations were conducted between 2000-2013 and the annual number continues to increase.[4] In Europe, countries such as the UK and Germany perform a combined total of approximately 30,000 ablations per year for atrial fibrillation (AF).[5,6]

For most arrhythmias treated by CCA, no convincing mortality benefit exists over medical therapy.[7-9] Therefore the clinical benefit for CCA lies in improvements in quality rather than quantity of life. In this context, validated health-related quality of life (HRQL) questionnaires, such as EuroQol-5D (EQ-5D) or Short form 36 (SF36), are a specific form of PROMs which are vital in assessing these improvements in a manner that is generalisable across treatments. [10]

PROMs Importance to system-level decision making

Organisations such as the UK's National Institute for Health and Care Excellence (NICE) routinely use EQ-5D and SF-36[11] to assess HRQL, employing them in comparative effectiveness research and cost-effectiveness analyses (CEAs). Accurate cost, clinical outcome, and HRQL data are all required as inputs for economic models used in CEAs. These are used to generate a cost per quality adjusted life year (QALY) associated with the treatment in question. Different treatments can subsequently be ranked

depending on the relative cost of gaining one QALY, thus informing health policy decisions. Although structures and parameters of economic models can be varied in a number of ways, in a previous sensitivity analysis of a model of CCA with no mortality benefit, HRQL were the dominant factor in the calculation of QALYs and cost-effectiveness.[12]

This review therefore sought to answer the following questions: How many RCTs of CCA include an assessment of PROMs, how frequently was this performed and which tools were used? What is the demography of patients included in RCTs of CCA and which patients report PROMs? What are the reporting standard of studies that include PROMs?

METHODS

The study protocol was registered on the PROSPERO online database (CRD42019133086) prior to search execution. The manuscript has been prepared according to the guidelines issued by the PRISMA group.[13] A checklist is available in the supplemental materials along with a list of protocol deviations.

Identification and Eligibility

We performed a comprehensive search using MeSH and free-text terms for various forms of the keywords 'catheter ablation' and 'cardiac ablation'. Medline, Embase, CENTRAL and WHO ICTRP (World Health Organization International Clinical Trials Registry Platform) databases were searched on 6 March 2019. The detailed search strategy is listed in the supplementary materials.

Studies were considered eligible if they satisfied the following criteria: English language RCTs assessing CCA of the heart in adult humans; for any of the following conditions: atrial fibrillation, atrial flutter, other SVTs (including atrioventricular node re-entrant tachycardia (AVNRT, accessory pathway and atrial tachycardias (AT)); ventricular ectopy and ventricular tachycardia; with at least 3 months of follow up. The following exclusion criteria were applied: studies where the primary aim was to compare the effect of adjunctive equipment or medication changes e.g. interrupted versus continuous anti-coagulation, use of amiodarone; oesophageal monitoring or where a further intervention was performed e.g. pacemaker implant or concomitant cardiac surgery.

Study selection and Data extraction

After removal of duplicates and clearly irrelevant records, two independent reviewers (YC, MN) screened the titles and abstracts of the search results. The full texts of the remaining results were individually assessed by both reviewers for inclusion with arbitration by a third author if necessary (PDL). A second stage of study selection used a "sense-check" of references of RCTs in existing systematic reviews of CCA to optimise the sensitivity of study identification. This is detailed in the supplemental materials.

Data was extracted from study reports independently and in duplicate by two reviewers (YC, MN) for each eligible study and included general characteristics of the RCTs, patient characteristics and reporting standards of PROMs where applicable.

PROMs Relevance

An algorithm originally developed and used by Rahimi et al[1] was adapted for the specific context of CCA, to assess the relevance of PROMs to each study. Studies were initially categorised as either pragmatic or exploratory – the definitions of each were in keeping with previous established methodology, described in greater detail in the supplementary material. This categorisation was the first stage in determining whether PROMs would be considered relevant to a study, with exploratory studies being less likely to be relevant. For example, a study by Di Biase et al[14] was defined as pragmatic given that it tested a hypothesis directly affecting decision-making and patient experience e.g. the choice between CCA or medical therapy; whereas Bulava et al[15] examined the effect of use of fluoroscopy which had little impact on overall decision-making or patient experience and therefore was defined as an exploratory study. Overall, we classified 177 RCTs as studies where PROMs were important, 56 RCTs where PROMs were of uncertain significance and only 4 where PROMs were likely irrelevant (Figure 2).

Reporting Standards

For RCTs that contained a patient reported outcome (PRO), the PRO-specific extension items from the CONSORT PRO statement were used to assess the reporting standard.[16] Two reviewers (YC, MN) independently scored each study, having calibrated their scoring sensitivity based on previous published work.[17] No disagreements remained after discussion.

Risk of Bias and Data synthesis

We did not conduct a risk of bias analysis since previous systematic reviews have already performed this in smaller subsets[18-21] and our study aims were focused around the prevalence, characteristics and

reporting standards of PROMs. We did not conduct any quantitative synthesis owing to the inherent heterogeneity of different study designs, follow up periods and types of PROMs used.

Patient and Public involvement

A focus day was held in March 2019 and attended by nine patients with AF. This helped to inform the scope of the research questions contained within this systematic review. One of the patients agreed to be a long term research partner for the first author and has contributed on a regular basis to this project, including critical review of both the study protocol and final manuscript.

RESULTS

Identified and Eligible studies

A total of 7,125 records were retrieved by the electronic search last updated on 6 March 2019 (3,864 study records and 3,261 trial registrations). Of 6,924 non-duplicate records, 6,348 irrelevant records were excluded after abstract review (Figure 1). We reviewed 576 full texts and excluded a further 339 studies. 237 RCTs therefore remained for analysis.

Characteristics of included studies

In total, 35,427 patients with a mean age of 59 years were included for analysis. 230 studies reported information on gender - 24,013/34,836 (69%) of patients were male. Only four studies[9, 22-24] reported data on ethnicity, although this included the largest RCT in the dataset, the CABANA trial.[9] In these four studies, 2,581/2,794 (92%) of patients were Caucasian. Reasonable assumptions could be made in certain studies about ethnicity depending on the study location – for example studies conducted in countries such as Japan or China. More detailed information including the type of arrhythmia and the intervention and comparators studied are outlined in Table 1. Comprehensive information regarding the individual characteristics of these studies are available in the supplementary materials.

PROMS prevalence and characteristics

PROMs were reported by 43 RCTs in total, representing 9,135 patients with a mean age of 61 years. 42/43 studies reported data on gender and 6,208/9,065 (69%) were male. Only 2/43 RCTs with PROMs reported ethnicity of which 2,228/2,414 (92%) were white. The average scheduled follow-up frequency was 2-3 times in 12 months. The most intensive PROMs schedules included follow up at baseline 3, 6, 9 and 12 months. Although the completion rate of PROMs was unclear in 9 studies, of the remaining 34, the average rate was 90%. Details on the type of PROMs and their follow up schedules are shown in Table 2. The generic HRQL questionnaire SF-36 was the most popular validated PROM used. In total, 27 studies included a generic PROM which measured HRQL that could be used in comparative effectiveness studies such as CEAs. More detailed information for each study is provided in the supplementary material. 12 RCTs included condition-specific HRQL questionnaires, with the Atrial Fibrillation effect on Quality of Life (AFEQT) being the most popular of those used. Although these can better capture different dimensions of treatment effects, they do not allow for calculation of a utility weighted QALY. In 5 RCTs, the PROMs reported were only a simple visual analogue score of pain. One study had yet to publish its quality of life data.[8] Therefore, 37 RCTs were assessed for their reporting standards of their included PROMs.

Reporting Standards of PROMs

The CONSORT PRO extension guidance document was used to assess reporting standards.[16] Table 3 outlines the individual score items along with the number of RCTs that fulfilled each criterion. No single study satisfied all the items and there was a wide range of adherence from 1-11 out of 14 individual criteria. The highest adherence was to the extension item (E15) at 89%. This is a non-specific part of the CONSORT PRO score, whereas the highest adherence to a specific CONSORT PRO part was item P1b (62%). Individual RCT scores are provided in the supplementary material.

Table 4 splits the studies into high (6-11), medium (3-5) and low ranges (1-2) of adherence to CONSORT PRO standards. For RCTs that were in the top tertile, there was increased use of validated PROMs that could be subsequently used in CEAs, as well as a longer follow-up time.

DISCUSSION

To our knowledge this is the first systematic review that captures the prevalence, characteristics and reporting standards of PROMs in RCTs of cardiac catheter ablation. Only 43/237 RCTs (18%) reported PROMs, and yet in at least 177 of those studies, PROMs were assessed to be important. Overall, many patients are under-represented in these trials. More than two thirds of patients were male and, where ethnicity was recorded, more than nine out of ten were Caucasian. These proportions were similar in the studies where PROMs were reported, highlighting that the root of the problem related to study recruitment rather than a systematic bias affecting differential collection or completion of PROMs. When collected, the average follow up frequency of PROMs was only between 2-3 times a year and the reporting standard was modest to poor with a range of 1-12 out of 14 CONSORT PRO items satisfied.

There are several important implications to our findings. Firstly, the selective representation of certain patient groups can significantly affect the generalisability of the current RCT evidence base. Given the studied population is predominantly middle-aged, white and male, conclusions about the relative benefit of CCA may not apply to patients who do not fit such a profile. For example, there is a body of literature which supports differential outcomes in HRQL depending on age and gender.[25,26] As the global burden of AF is increasingly recognised as having gender parity[27], there is a risk that the patients recruited to RCTs, and the PROMs that are collected, are not reflective of the population being treated. This has significant implications for counselling patients on the potential benefits to their HRQL when undergoing CCA.

Secondly, for most patient groups, given the absence of convincing evidence for mortality benefit of CCA[7-9], PROMs are a critical factor in the calculation of its cost-effectiveness. Importantly, the studies in this review included a wide range of different ablation techniques. Any relative differences in HRQL

between these interventions, and the associated impact on subsequent CEAs, would help to identify which techniques provide the most benefit to patients and value for money to the healthcare system.

A challenge for PROMs specific to cardiac arrhythmias are in circumstances where a high frequency of debilitating symptoms due to arrhythmia recurrence could potentially outnumber the frequency of assessment of PROMs during follow up. Subsequent snapshot values when aggregated to inform a QALY may miss short term penalties in HRQL owing to recall bias.[28] Given that CEAs often model the effects treatments over a patient's lifetime[29], small differences in HRQL can magnify dramatically over time. A systematic review of existing CEAs in AF additionally highlighted how selective quotation of the paucity of HRQL data – particularly disease specific PROMs – can limit the generalisability and validity of conclusions made.[30]

Better reporting of PROMs could resolve such issues and widespread collection could potentially allow enough data for subgroup analysis to be made for the benefit of clinicians, policymakers and patients. For example, many patients undergo CCA as a second procedure, particularly in AF.[6] The effect of second or third CCA on HRQL and the relative impact compared to lifestyle modification or continuing medical therapy represent important questions to answer in the future.

Moving forward, the timeliness of better PROMs collection also coincides with rapid adoption of technological solutions – often instigated by patients themselves – which can reduce the barrier to implementation in clinical studies. The use of wearable devices continues to grow[31], however, one risk that needs to be considered is the potential worsening of representativeness through the digital exclusion of certain patient subgroups. Of note, no study in our review included details about the socioeconomic status of patients. Given the association between social deprivation and poorer health outcomes[32], a unified effort across professional boundaries is needed to ensure that all patients have access to treatments as well as the means by which they can report how these treatments impact on their quality of life.

Limitations

Our findings must be considered in the light of several limitations. Firstly, although our search strategy was comprehensive, and covered multiple databases, studies may have been missed. We did not search grey literature or non-English sources given the large number of included studies for review as this was not anticipated to have a significant impact on our findings.

Secondly, the intentional exclusion of studies of catheter ablation which had additional pacemaker or defibrillator implantation or concomitant surgery has missed studies with PROMs data.[33,34] However, such additional procedures would have diluted the effect of catheter ablation on patient HRQL, therefore making it difficult to disentangle the effects on HRQL that is purely due to ablation.

Thirdly, we restricted our study sample to RCTs only. A previous systematic review of CCA of AF[35] highlighted that 138 of 174 studies (79%) were observational or used a non-randomised design, with many examples of PROMs included in such studies.[36] However, our review focused on RCTs given that this is the gold standard study design which the research community uses to answer important clinical questions. From a monetary perspective, RCTs are expensive and the direct and indirect costs of conducting RCTs are well-reported.[37] Ensuring that RCTs include reliable PROMs which matter to patients is an important consideration in delivering value and reducing research waste where important outcomes relevant to users of research are not being assessed.[38]

CONCLUSION

The current standard of PROMs collection and reporting in RCTs of cardiac catheter ablation is poor. There is cause for optimism however, given that PROMs were included as the primary endpoint in a prominent trial of AF ablation recently.[39] Researchers and clinicians should leverage the increasing popularity of wearable technologies to ensure that PROMs are easier to integrate into future trial designs. Although cardiac catheter ablation has been used as an exemplar to highlight the deficiencies of PROMs in RCTs, their importance is applicable to all areas of cardiology and the wider medical community,

particularly when examining treatments where the benefit conferred to patients is symptomatic improvement. Greater use of validated PROMs will ensure that the calculation of the clinical and cost-effectiveness of proposed treatments are more robust and generalisable. This will serve to help equip patients, clinicians and policy makers alike with actionable data that will better inform decision making.

Author Contributions

YC and PDL conceived the study and wrote the study protocol. PW and MG contributed to critical revision of the protocol. MN created the search strategy. YC and MN collected the data and wrote the first draft of the manuscript. RR contributed to analysis and presentation of the PROMs reporting. MG, RR and PW contributed to critical revision of the manuscript. All authors subsequently contributed to further revision and approve the final version. PDL is the guarantor

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Table legends

Table 1. Summary characteristics of RCTs included for qualitative analysis**.** a) In one study, the published supplement and study protocol referred to PROMs including EQ-5D but these remain unpublished.

Table 2. Summary characteristics of the types of PROMs in RCTs that included them, separated by condition studied.

Table 3. PROs-specific extensions are prefaced by the letter P; PROs-specific elaborations are prefaced by the letter E. PROs, patient-reported outcomes. The scores are 'all or nothing' as per previous scoring methodology.

Table 4. Breakdown of RCTs into tertiles of High, medium and low adherence to CONSORT PRO. a) 3/9 RCTs had unclear follow up schedules

Figure legends

Figure 1. PRISMA Flow of study records

Figure 2. Flow diagram used to determine whether the presence of PROMs in the trial design was important, uncertain or irrelevant, depending on pre-categorisation into either Pragmatic (A) or Exploratory (B) trial design.

APPENDIX 1 – SEARCH STRATEGY

Medline and Embase (OvidSP)

1) randomized controlled trial.pt
2) controlled clinical trial.pt
3) randomized.ab
4) placebo.ab
5) drug therapy.fs
6) randomly.ab
7) trial.ab
8) groups.ab
9) or/1-8
10) exp animals/ not humans.sh
11) 9 not 10
12) (heart or cardiac or cardio* or electrophysiology or node or atrioventricular or atria* or ventric* or flutter or vt or af or accessory pathway).ti
13) ablation.ti
14) (radiofrequency or rf or cryoablation).ti
15) pulmonary vein isolation.ti
16) catheter ablation/
17) or/13-16
18) 11 and 12 and 17
19) DEDUPLICATE 18

→ 3,864 records on 6 March 2019

CENTRAL (Cochrane Central Register of Controlled Trials) (Wiley)

#1. (ablation):ti,ab

#2. (radiofrequency or rf or cryoablation):ti,ab

#3. (pulmonary vein isolation):ti,ab

#4. MeSH descriptor: [Catheter Ablation] explode all trees

#5. #1 OR #2 OR #3 OR #4

#6. (heart or cardiac or cardio* or electrophysiology or node or atrioventricular or atria* or ventric* or flutter or vt or af or accessory pathway):ti,ab,kw

#7. #5 AND #6

#8. #7 in Trials

→ **2,630 records on 6 March 2019**

WHO ICTRP (available at http://apps.who.int/trialsearch/)

- (ablation or pulmonary vein or pvi or rf or radiofrequency or cryoablation) in TITLE
- (heart or cardiac or cardio* or electrophysiology or node or atrioventricular or atria* or ventric* or flutter or vt or af or accessory pathway) in CONDITION
- PHASES limited to 3 or 4; RECRUITMENT STATUS is all

→ **(631 records) from 472 trials on 6 March 2019**

Due to the large number of studies to be screened, an additional check was conducted to minimize studies being missed that fulfilled inclusion criteria that was not immediately obvious on title and abstract review. An additional sense check search was conducted on 26 September 2019. On PubMed, the term "catheter ablation" was searched with the filters: systematic review, humans and within last 5 years.

This generated a list of 178 results which were screened for relevant systematic reviews. Seven were identified[1-7] which were then subsequently analyzed to detect any RCTs that fulfilled our inclusion criteria. No RCTs were found that were not identified in our original searches.

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APPENDIX 2 – PROTOCOL DEVIATIONS & CLARIFICATIONS

1. Scope of review

We limited the analysis to exclude cost-effectiveness studies: after initial abstract review, it was decided that the focus of the study was to give an in-depth treatment of the clinical academic literature rather than studies which were more likely aimed at a health economic readership. This had a subsequent impact on the objectives which were changed to remove the following:

- In Cost effectiveness analysis studies based on RCT data, what proportion rely on a mixture of expert opinion and PROMs versus PROMs alone?
- Is there a difference in cost-effectiveness outcome between studies that have a low intensity of HRQL measurement versus those with a high intensity?
- Is there a difference in cost-effectiveness outcome between studies that have rely on a mixture of expert opinion and PROMs versus PROMs alone?

These were replaced with or amended to:

- When HRQL is reported, what was the demographic of patients that did so?
- Which tool was used to assess HRQL, and how many of these are validated tools?
- How frequently was HRQL assessed?
- What is the reporting quality of studies that include patient-reported HRQL?

Although quality of life is affected by domains outside of health, we have not considered this for the sake of simplicity as well as ensuring the perspective is focused on health-related rather than societal (e.g. impact on personal economic situations related to unemployment).

2. Amendments to additional searches:

The change in emphasis of the scope of the review also caused a modification of the additional searches. Originally, the intention was to identify cost effectiveness analyses via a reverse citation search on Google Scholar. This was replaced with an additional sense check search conducted on 26 September 2019. On PubMed, "catheter ablation" with the filter systematic review, humans and within last 5 years generated a list of 178 results which were screened for relevant systematic reviews which were then subsequently checked to identify any RCTs missed by the original search or by either reviewer.
In addition, given the large number of study results and the breadth of the review, we decided not to proceed with either contacting authors of included studies (the need arose mainly from clinical trial registrations with unclear documentation of whether studies had completed or published their work)[1] or reference searching of included studies to identify further studies.

3. Amendments to study inclusion criteria:

There were minor changes to the listed cardiac conditions – the original term "AV node and accessory pathway" was replaced with "Other SVT (including AVNRT, Accessory pathway and AT)"
There was also expansion of the comparator to include studies that examined a different ablation technique, rather than studies that examined only catheter ablation vs. medical therapy.

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APPENDIX 3 – RELEVANCE OF PROMS

We used work by Rahimi et al[1] to develop a tailored assessment of the relevance of PROMs in RCTs of Cardiac Catheter ablation. In brief, Rahimi's group describe previous work in the area,[2-6] outlining relevant factors when making such a judgement, and after piloting, relevant features were ranked and operationalized into a decision-tree to include factors such as: study objective; type(s) of primary outcome measures and their importance from patients' perspective. In the original methodology, the level of importance of PROMs to clinical decision making was ordered into five categories (crucial, important, potentially relevant, irrelevant and uncertain), mirroring work by Veldhuyzen van Zanten.[7]

We have simplified this to important, uncertain and irrelevant for the purposes of our study. This is in part because our study focuses solely on cardiac catheter ablation where the relevance of PROMs should in the main be important (given that the treatment has only been shown to confer symptomatic improvement for patients). Before categorization of the selected studies, our study group considered that smaller RCTs may be more mechanistic in terms of their outcomes measured. Our pre-specified inclusion criteria was for a minimum of 3 months of follow up to filter out such studies but we included irrelevant and uncertain categories to accommodate studies with adequate follow up that were answering a purely mechanistic question e.g. effect of using different types of catheter tips on ablation indices.[8]

The definition of whether a study was pragmatic or explanatory followed previous methodology:

"If a study primarily sought to test a hypothesis useful for understanding the differences between intervention strategies without any claims on changing clinical practice, it was considered explanatory. Whereas studies aiming to help making decision about alternative strategies were categorized as pragmatic trials."[9]

PROMs were considered as either irrelevant, uncertain or important in explanatory trials; whereas in pragmatic trials PROMs were considered only as either uncertain or important.

Here the distinction arose because of the fact that most included studies tended to measure physiological or surrogate outcomes such as recurrence of arrhythmia or arrhythmia burden as their primary outcome. For pragmatic trials, our contention was that a PROM would always be either important or at the very least of uncertain significance depending on the exact nature of the primary outcome. For explanatory trials, only four studies were deemed to have outcomes which meant PROMs were not relevant [Figure 2].[8,10-12]

The flowchart outlines the logic of this and the definition of an outcome important to patient is as follows: "Patient-important outcomes incorporate all outcomes that directly impact on patient's well-being or health status. Ferreira-Gonzales et al[3] previously reported a ranking system for trial outcomes according to their importance to patients - categorized into five groups: (i) death, (ii) critical (e.g. large myocardial infarction), (iii) major (e.g. non-fatal myocardial infarction), (iv) moderate (e.g. admission to hospital), and (v) minor (e.g. change in blood pressure)."

We considered the first four categories as patient important outcomes as well as any study which reported adverse events including drug discontinuation or complications related to the ablation which required extended length of stay e.g. cardiac tamponade.

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APPENDIX 4 – LIST OF STUDIES WITH PROMs

Author	Funding	Type of PROMs used	P1b	P2a	P2b	P4a	P6a	P7a	P12a	P13a	P15	P16	P17a	P18	P20/21	P22	Total
Atienza et al 2014	Mixed	AF QoL	1	0	0	n/a	0	n/a	0	0	1	0	1	n/a	0	0	3
Blomstrom-Lundqvist et al 2019	Mixed	**SF-36**	1	1	0	n/a	1	1	1	1	1	1	1	1	1	1	11
Boersma et al 2016	Industry	AF symptom severity score	0	0	0	n/a	0	n/a	0	0	1	1	1	n/a	0	0	3
Chan et al 2011	None	VAS	1	0	0	n/a	0	0	n/a	1	n/a	1	n/a	n/a	1	1	5
Collins et al 2006	.	VAS	1	1	0	n/a	0	0	n/a	1	n/a	1	n/a	n/a	1	0	5
Darkner et al 2014	Mixed	**SF-36**	0	0	0	n/a	0	n/a	0	0	1	0	0	n/a	0	0	1
Deisenhofer et al 2010	Industry	VAS	1	0	0	n/a	0	n/a	n/a	1	n/a	1	n/a	n/a	0	1	4
Di Biase et al 2016	.	MHLFQ	0	1	0	n/a	1	n/a	0	0	1	1	1	n/a	0	0	5
Forleo et al 2009	Unclear	**SF-36**	1	0	0	n/a	0	n/a	1	0	0	1	0	n/a	0	0	3
Gula et al 2018	Mixed	**SF-36, EQ-5D**, ICDC, HADS	1	1	1	n/a	1	n/a	1	0	1	1	1	1	1	1	11
Gupta et al 2007	Charity	**SF-36** and modified Karolinska	1	0	0	n/a	0	n/a	1	1	1	1	1	n/a	0	0	6
Hummel et al 2014	Industry	Unvalidated symptom severity and QoL forms	0	0	0	n/a	1	n/a	0	0	1	0	0	n/a	0	0	2
Hunter et al 2014	Charity	**SF-36** and MHLFQ	1	0	0	n/a	0	n/a	0	1	1	1	1	n/a	0	0	5
Jais et al 2008	Unclear	**SF-36**	1	0	0	n/a	0	n/a	0	0	0	0	0	n/a	0	0	1
Jones et al 2013	.	MHLFQ	1	1	0	n/a	0	n/a	1	1	1	1	1	n/a	0	1	8
Khaykin et al 2009	Unclear	**SF-36**	0	0	0	n/a	0	n/a	1	0	1	1	1	n/a	0	0	4
Kuck et al 2016	Industry	**SF-12, EQ-5D-3L**	1	1	0	n/a	0	n/a	1	0	1	1	1	n/a	0	0	6
Lau et al 1995	Academic	General Health Questionnaire, Somatic Symptoms inventory, Sickness Impact Profile, Subjective concerns	1	1	0	n/a	1	n/a	1	0	1	1	1	n/a	1	1	9
MacDonald et al 2011	Academic	**SF36,** KCCQ, MLHFQ	0	0	0	n/a	0	n/a	1	1	1	1	1	n/a	0	1	6
Malmborg et al 2013	Academic	**SF-36,** Symptom scale	1	1	0	n/a	0	n/a	0	0	0	0	1	n/a	0	0	3
Mantovan et al 2013	Commercial	**SF-36**	1	1	1	n/a	1	n/a	1	0	1	0	1	1	1	1	10

Mark et al 2019	Mixed	AFEQT, MAFSI, AFSS, **SF-36, EQ-5D-3L,** Stanford Presenteeism Scale, and Work Productivity and Activity Impairment Questionnaire	1	1	0	n/a	1	n/a	0	1	1	1	1	1	1	1	10
Marrouche et al 2018*	Commercial	N/A	0	0	0	n/a	0	0	0	0	0	0	0	0	0	0	0
McLellan et al 2015	Academic	**SF-36,** CCS-AF	0	0	0	n/a	0	n/a	0	0	1	1	0	n/a	0	0	2
Mohanty et al 2013	Unclear	**SF-36,** BDI, STAI, HAD	1	1	0	n/a	1	n/a	0	0	1	0	1	n/a	1	0	6
Mont et al 2014	Commercial	AF-QOL	0	0	0	n/a	0	n/a	0	0	1	0	1	n/a	1	0	3
Morillo et al 2014	Mixed	**EQ-5D**	1	1	0	n/a	0	n/a	0	0	1	0	0	n/a	1	0	4
Mortsell et al 2018	Academic	SSQ, **EQ-5D**	1	0	0	n/a	0	n/a	0	0	1	0	1	n/a	0	0	3
Natale et al 2011	Academic	Endicott, Quality of Life Enjoyment and Satisfaction Questionnaire	1	0	0	n/a	1	n/a	0	0	1	0	0	n/a	0	0	3
Nielsen et al 2017	Mixed	**SF-36,** ASTA	1	1	0	n/a	0	n/a	0	0	1	0	1	n/a	1	1	6
Oral et al 2006	Academic	Unvalidated severity of symptom questionnaire	0	0	0	n/a	0	n/a	0	0	1	0	0	n/a	0	0	1
Packer et al 2013	Commercial	**SF-36**	0	0	0	n/a	0	n/a	0	0	1	0	0	n/a	0	0	1
Pappone et al 2011	Academic	**SF-36**	1	1	0	n/a	0	n/a	0	0	1	0	0	n/a	1	0	4
Podd et al 2015	Academic	**SF-36**	0	0	0	n/a	0	n/a	0	0	0	0	1	n/a	0	0	1
Prabhu et al 2017	Academic	**SF-36**	0	0	0	n/a	0	n/a	0	0	1	1	1	n/a	0	0	3
Reddy et al 2015	Commercial	AFEQT	0	0	0	n/a	0	n/a	0	0	1	1	0	n/a	0	0	2
Sohara et al 2016	.	**SF-36**	0	0	0	n/a	0	n/a	0	0	1	0	1	n/a	1	1	4
Thornton et al 2008	.	VAS	0	0	0	n/a	0	n/a	0	0	0	0	0	n/a	0	0	0
Timmermans et al 2003	Unclear	VAS	1	1	0	n/a	1	n/a	0	0	0	1	0	n/a	1	0	5
Wazni et al 2005	Industry	**SF-36**	1	1	0	n/a	1	n/a	0	0	1	1	1	n/a	1	0	7
Wilber et al 2010	Industry	**SF-36,** AF Symptom Frequency and Severity Checklist	1	1	1	n/a	1	n/a	1	0	1	1	1	n/a	0	1	9
Wynn et al 2016	.	AFEQT, **SF-36**	1	0	0	n/a	0	n/a	0	0	1	0	0	n/a	0	0	2
Zhang et al 2014	Academic	**SF-36**	1	1	0	n/a	1	n/a	1	0	1	0	0	n/a	1	1	7

Table A5. Individual scores of studies which included a PROM on CONSORT PRO. Rows shaded in blue indicate studies which used only a simple visual analogue score and did not use a validated PROM tool to assess QoL. In the column 'Types of PROMs used', those in bold indicate PROMs that may be used in economic analyses of cost-effectiveness. *The study by Marrouche et al has yet to publish its QoL data at the time of writing. MHLFQ= Minnesota living with heart failure questionnaire, EQ-5D = EuroQol 5D, VAS = visual analogue scale, ICDC – ICD concerns questionnaire, HADS= Hospital anxiety and depression scale, KCCQ = Kansas city cardiomyopathy questionnaire, AFEQT = Atrial Fibrillation effect on quality of life, MAFSI = Mayo AF specific symptom inventory, AFSS = Atrial fibrillation severity scale, BDI = Beck depression index, STAI = state trait anxiety inventory, SSQ = Symptom severity questionnaire, ASTA = Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia

Funding

11 RCTs were Industry or Commercially funded, 7 were mixed, 11 were Academic, 2 were Charity and 1 declared nil funding required. Only 11 studies (26%) had unclear or no information regarding their funding status, which compared favourable to the overall study dataset where 121/237 (51%) had unclear or no information.

APPENDIX 5 – CONSORT PRO Extension statement

Table 1. Information for Reporting Randomized Controlled Trials With Patient reported Outcomes

Section/Topic	Item	CONSORT 2010 Statement Checklist Item	PRO-Specific Extensions Are Prefaced by the letter *P*
		Title and Abstract	
	1a	Identification as a randomized trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[3]	P1b: The PRO should be identified in the abstract as a primary or secondary outcome
		Introduction	
Background and objectives	2a	Scientific background and explanation of rationale	Including background and rationale for PRO assessment
	2b	Specific objectives or hypotheses	P2b: The PRO hypothesis should be stated and relevant domains identified, if applicable
		Methods	
Trial design	3a	Description of trial design (such as parallel, factorial), including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	Not PRO-specific, unless the PROs were used in eligibility or stratification criteria
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	P6a: Evidence of PRO instrument validity and reliability should be provided or cited if available including the person completing the PRO and methods of data collection (paper, telephone, electronic, other)
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	Not required for PRO unless it is a primary study outcome
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
		Randomization	
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomization; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	P12a: Statistical approaches for dealing with missing data are explicitly stated
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
		Results	
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	The number of PRO outcome data at baseline and at subsequent time points should be made transparent
	13b	For each group, losses and exclusions after randomization, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Including baseline PRO data when collected
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Required for PRO results
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, the estimated effect size, and its precision (such as 95% confidence interval)	For multidimensional PRO results from each domain and time point
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	Including PRO analyses, where relevant
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
		Discussion	
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	P20/21: PRO–specific limitations and implications for generalizability and clinical practice
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	PRO data should be interpreted in relation to clinical outcomes including survival data, where relevant
		Other Information	
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

Reproduced from *Reporting of Patient-Reported outcomes in Randomized Trials: The CONSORT PRO Extension. JAMA, February 27, 2013_Vol309(8)*

APPENDIX 6 – PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	**1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	**3**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	**5-6**
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**6**
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	**7**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	**7**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**7 and Appendix 1**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**Appendix 1**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**7-8**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**8**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**Appendix 2-5**
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**N/A**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	**N/A**

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	**N/A**
Section/topic	#	Checklist item	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**N/A**
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	**N/A**
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**10 & Figure 1**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**Table 1 & Appendix 3**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	**N/A**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	**Table 1-3**
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	**N/A**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	**N/A**
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	**N/A**
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	**12-14**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	**14**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**14-15**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	**15**

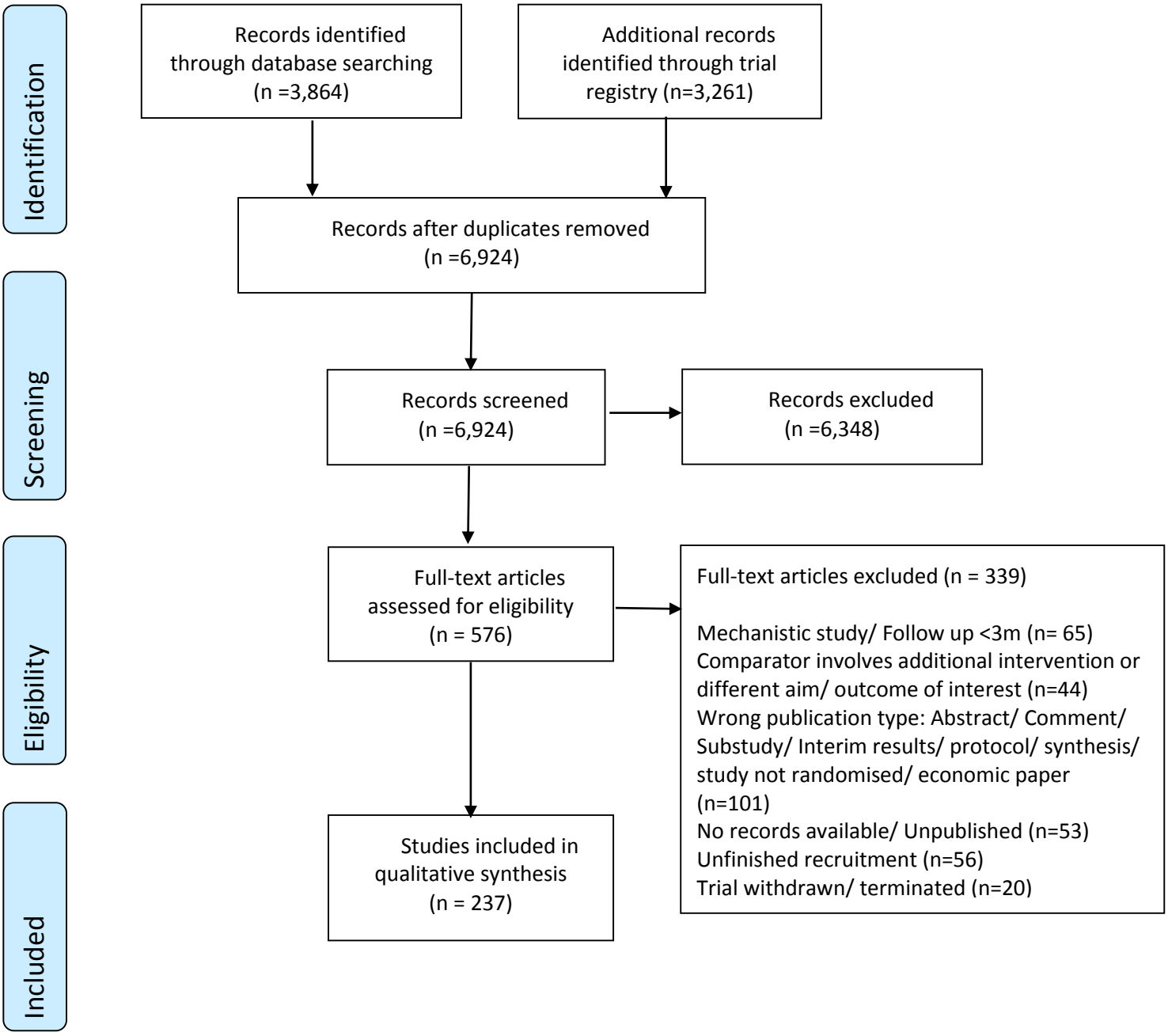
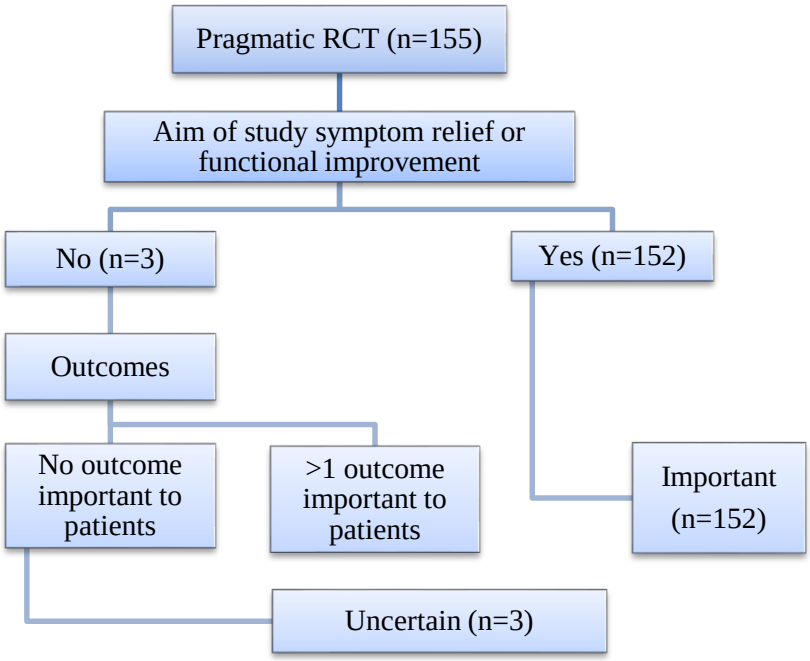


Figure 1. PRISMA Flow of study records

A – Pragmatic



B – Exploratory

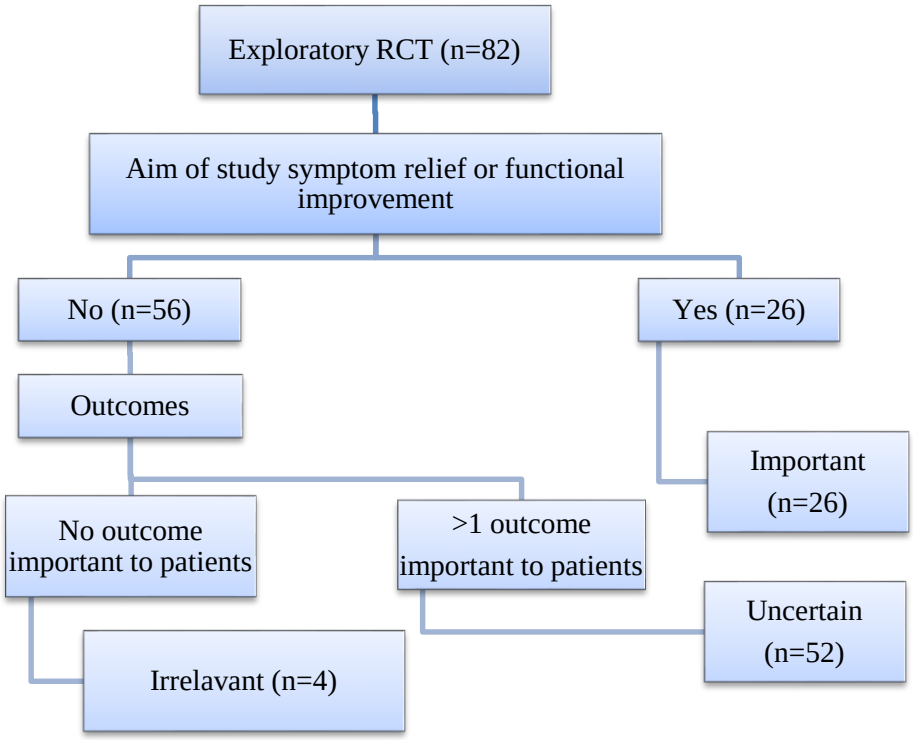


Figure 2. Flow diagram used to determine whether the presence of PROMs in the trial design was important, uncertain or irrelevant, depending on pre-categorisation into either Pragmatic (A) or Exploratory (B) trial design.

Condition studied	Intervention and Comparator	Centre	Geography	Funding	Inclusion of PRO	Year of publication
Paroxysmal AF (n=73)	Ablation technique vs. AAD (n= 31)	Single (n=160)	Europe (n=134)	Not mentioned/ unclear (n=122)	None (n=194)	2018-2019 n=27
Paroxysmal AF and Persistent AF (n=45)	Ablation technique 1 (PVI) vs. Ablation technique 2 (PVI) (n=67)	Multicenter (n=77)	N America (n=30)	Academic (n=54)	Validated form (n=32)[a]	2016-2017 n=32
Persistent, Long standing Persistent and Permanent (n=42)	Ablation technique 1 (involves PVI+ additional lesion) vs. Ablation technique 2 (any other) (n=73)		Asia (n=44)	Industry/ Commercial (n=35)	Unvalidated form (n=6)	2014-2015 n=51
Mixed AF (n=12)	Ablation involving CTI in both arms (n=31)		S. America (n=1)	Charity (n=3)	Other e.g. self-reported pain on a measured scale (n=5)	2012-2013 n=26
SVT (including AVNRT, Accessory pathway and AT)	Ablation technique vs. staged DCCV +/- ablation		Australasia (n=4)	Mixed (n=17)		2010-2011 n=22

(n=21)	(n=6)					
Atrial Flutter (n=34)	Other (n=29)		Africa (n=1)	No funding (n=6)		2008-2009 n=30
Atrial Flutter and Atrial Fibrillation (n=3)			>2 continents (n=23)			≤2007 n=49
VT or VEs (n=7)						

Table 1. Summary characteristics of RCTs included for qualitative analysis. a) In one study, the published supplement and study protocol referred to PROMs including EQ-5D but these remain unpublished.

Condition studied	Type of PROM	Mean follow up	Average PROMs schedule (per 12 months)
Paroxysmal AF (n=13)	• 12/13 used validated forms (SF36, SF-12, EQ-5D, AFEQT, AF-QoL)	22 months	x3.1
Paroxysmal AF and Persistent AF (n=11)	• 11/11 used validated forms (EQ-5D, SF36, AF-QoL, SSQ, AFEQT, MAFSI, MLWHFQ)	22 months	x2.4
Persistent, Long standing Persistent and Permanent (n=9)	• 8/9 used validated form (SF-36, KCCQ, MLHFQ)	11 months	x2.9
SVT (including AVNRT, Accessory pathway and AT) (n=4)	• 2/4 used validated form (SF-36) • 2/4 used visual analogue pain score	12 months	x2.1
Atrial Flutter (n=4)	• 1/4 used validated form (SF-36 and Q-LES-Q) • 3/4 used visual analogue pain or verbal pain score	12 months	x3
Atrial Flutter and Atrial Fibrillation (n=1)	• 1/1 used validated form (SF-36)	12 months	x2
VT or VEs (n=1)	• 1/1 used validated form (SF-36, KCCQ, MLHFQ, AF-QoL, EQ-5D)	23 months	x3

Table 2. Summary characteristics of the types of PROMs in RCTs that included them, separated by condition studied.

Descriptor of the 2013 CONSORT PRO-specific extension or elaboration.	**Number of trials where item was adequately reported, n (%)**
P1b Identification of the PROs in the abstract as a primary or secondary outcome	23/37 (62%)
E2a Background and rationale for PROs assessment	16/37 (43%)
P2b Identification of the PROs relevant domains Statement of the PROs hypothesis Statement of the PROs analysis power	3/37 (8%)
E4a Eligibility criteria. Not PRO specific unless they were used in eligibility or stratification criteria	N/A
P6a Evidence of PROs instrument validity Reference of the PROs instrument Statement of the person completing the PROs Methods of data collection (paper, telephone, electronic, other)	12/37 (32%)
E7a Sample size calculation. Not required for PRO unless it is a primary study outcome	1/1 (100%)
P12a Statistical approaches for dealing with missing data are explicitly stated	12/37(32%)
E13a Description of the number of PROs outcome data at baseline and at subsequent time points	6/37 (16%)
E15 Table showing baseline characteristics. Including baseline PROs data when collected	33/37 (89%)

E16 For each group, number of participants (denominator) included in each analysis. Required for PROs results	18/37 (49%)
E17a For each primary and secondary outcome, results for each group, the estimated effect size, and its precision. For multidimensional PROs results from each Domain	24/37 (65%)
E18 Results of ancillary analyses. Including PRO analyses where relevant	4/4 (100%)
P20/21 PROs-specific limitations and implications for generalizability and clinical practice	13/37 (35%)
E22 PROs data should be interpreted in relation to clinical outcomes including survival data	11/37 (30%)

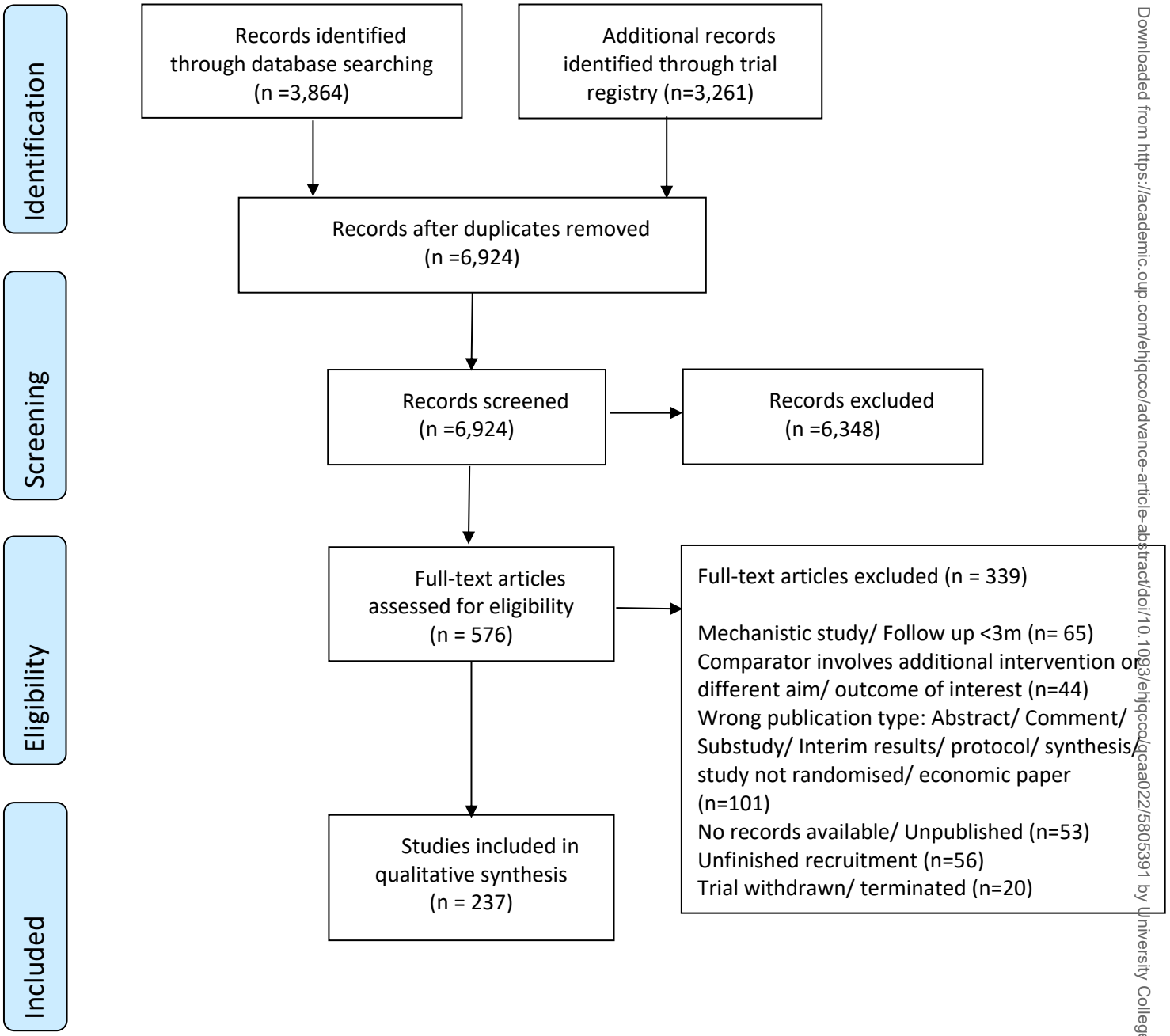
Table 3. PROs-specific extensions are prefaced by the letter P; PROs-specific elaborations are prefaced by the letter E. PROs, patient-reported outcomes. The scores are 'all or nothing' as per previous scoring methodology.

	High adherence N=14 (%)	**Medium adherence N=14 (%)**	**Low adherence N=9 (%)**
Average score	8 (57)	4 (29)	1 (11)
Number of PROMs specific papers	6 (43)	1 (7)	0 (0)
Number RCTs with >1 HRQL questionnaires	9 (64)	2 (14)	2 (22)
Number of RCTs with generic HRQL e.g. EQ-5D or SF-36	12 (86)	9 (64)	6 (67)

Number of RCTs that did not use a validated HRQL questionnaire	1 (7)	3 (21)	2 (22)
Average frequency of follow up in 12 months	2.9	2.4	3.6[a]
Average length of follow up	24 months	17 months	11 months

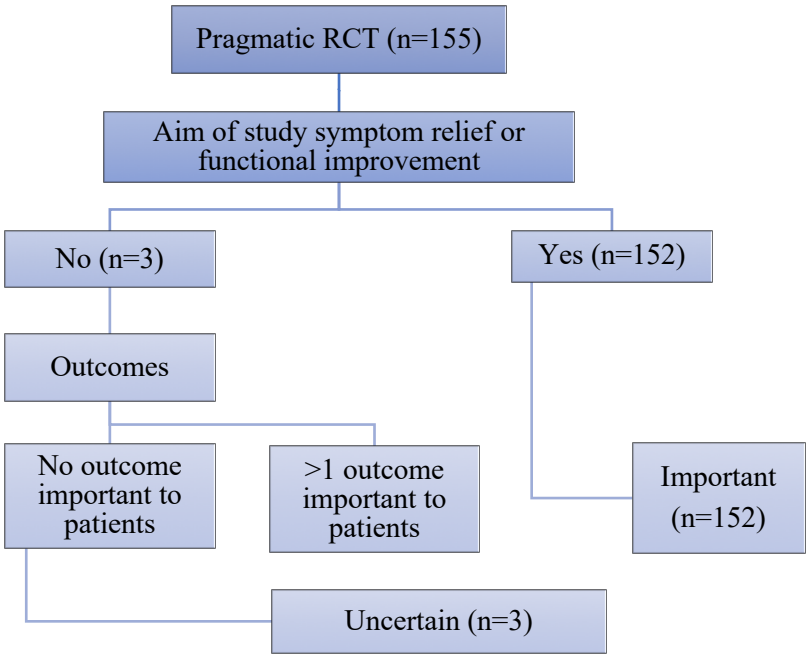
Table 4. Breakdown of RCTs into tertiles of High, medium and low adherence to CONSORT PRO. a) 3/9 RCTs had unclear follow up schedule

Figure



Figure

A – Pragmatic



B – Exploratory