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Santé-AF Sessions of Acupuncture and Nutritional Therapy Evaluation for Atrial Fibrillation

Feasibility study to inform a randomised controlled trial

Sessions of Acupuncture and Nutritional Therapy Evaluation for Atrial Fibrillation (Santé-AF)

A feasibility study to inform a randomised controlled trial

Study protocol v1.5

COVID-19 adaptations highlighted in blue

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1.1 Abbreviations

AED	Ambulatory ECG device (the CardioSTAT® monitor manufactured by Icentia Limited)
AF	Atrial fibrillation
BAcC	British Acupuncture Council
BANT	British Association of Nutritional Therapy and Lifestyle Medicine
EOI	End of Intervention
INR	International Normalised Ratio, a measure of blood clotting time (anticoagulation)
NCA	Northern College of Acupuncture (the study centre)
PPI	Patient and Public Involvement
PT	Prothrombin time, a measure of blood clotting time (anticoagulation)
TSC	Trial Steering Committee

1.2 Protocol version history log

Version and date	Approvals	Details of significant changes
Version 1.0 3rd March 2020	Dr Judith Watson Professor David Torgerson	First version
Version 1.1 11th May 2020	Dr Judith Watson Professor David Torgerson Dr Sanjay Gupta Professor Hugh MacPherson	Amends and clarifications to first version, for NHS REC resubmission
Version 1.2 24th June 2020	Dr Judith Watson	Amends and clarifications to second version, for NHS REC sreubmission
Version 1.3 30th November 2020	Dr Judith Watson	Minor edits
Version 1.4 15th December 2020	Dr Judith Watson	COVID-19 adaptations classed as non-substantial amendments (see HRA guidance at https://www.hra.nhs.uk/covid-19-research/covid-19-guidance-sponsors-sites-and-researchers/)
Version 1.5 27th February 2021	Dr Judith Watson	COVID-19 adaptations classed as substantial amendments requiring REC approval (see HRA guidance at https://www.hra.nhs.uk/covid-19-research/covid-19-guidance-sponsors-sites-and-researchers/)

2 Abstract

Background: Atrial fibrillation (AF) is a common cardiac rhythm disturbance associated with significant increase in the risk of stroke; incidence is increasing globally. Current clinical guidelines for AF focus on preventing complications and alleviating symptoms. Additionally, recent research suggests that patients with atrial fibrillation experience a degradation of their health-related quality of life in proportion to perceived symptoms. A small body of evidence suggests that traditional acupuncture and nutritional therapy may improve quality of life and symptoms for patients with AF; a high-quality trial is indicated. To test the feasibility of a future trial, a small feasibility study is proposed.

Aim: To test the feasibility of several aspects of a future trial's design.

Objectives: To evaluate: participants' willingness to be randomised; the appropriateness of eligibility criteria; participant retention; acceptability of interventions; acceptability of participant assessments; effect of ambulatory ECG devices (AEDs); participant experience of study participation (including practitioner experience); and the feasibility of all objectives during a global pandemic.

Design: Pragmatic three-arm parallel randomised controlled feasibility study incorporating Acupuncture + Usual Care (Group A); Nutritional Therapy + Usual Care (Group B); Usual Care alone (Group C). Participants will be allocated to each group on a 2:2:1 allocation ratio in favour of the interventions. Note that this trial is a feasibility study and therefore outcome measures are applied not to obtain effectiveness data but to test for feasibility.

3 Study information

3.1 Study personnel

- **Researcher:** Karen Charlesworth (KC), Northern College of Acupuncture, 61 Micklegate, York YO1 6LJ.
- **Chief Investigator and researcher's academic supervisor:** Dr Judith Watson (JW), Department of Health Sciences, University of York YO10 5DD.
- **Study sponsor:** The University of York (Department of Health Sciences)
- **Study sponsor's representative:** Dr Michael Barber, Contracts and Sponsorship Manager, Research and Enterprise Directorate, University of York, Heslington, York YO10 5GE.
- **Consultant cardiologist** to the feasibility study: Dr Sanjay Gupta (SG).
- **Trial Steering Committee**
  Chair: Harriet Lansdown, MBAcC (HL).
  Acupuncturist member: John Wheeler MBAcC (JW).
  Nutritional therapist member: Dr Sonia Williams MBE (SAW).
  Cardiologist member: Dr Sanjay Gupta (SG).
- **Supply of CardioSTAT® ambulatory ECG devices (AEDs) and device data processing services:** Icentia Limited, York Science Park Innovation Centre, Innovation Way, Heslington, York YO10 5NY. Director: Darren Macfarlane.
- **Patient and Public Involvement panel**:
  Lay person: Eamonn Anderson (Chartered Accountant), Main Street, Wheldrake, York.
  Patients have requested to remain unnamed for confidentiality reasons.
- **Therapy Advisory Panel members:**
  Acupuncture: Cheng Hao Zhou (CHZ); Harriet Lansdown (HL)
  Nutritional Therapy: Dr Jane Jamieson (JJ); Sally Duffin (SD), Dr Sonia Williams (SAW), Jane Nodder (JN)
- **Administrators** otherwise unconnected with the study: Michelle Bowie (MB), Marie Clarkson (MC), Abby Foreman (AF)

3.2 Registration details

ISRCTN: 13671984

3.3 Sources of funding and other support

Funding has been given by two bodies:

The British Acupuncture Council (BAcC), 63 Jeddo Road, London W12 9HQ. Funding amount: £10,000.

The Northern College of Acupuncture (NCA), 61 Micklegate, York YO1 6LJ. Funding amount: £5,204 of support in kind.

3.4 Ethical approval details

Ethical approval has been given by:

- The University of York Health Sciences Research Governance Committee (decision letter HSRGC/2019/346/H)
- NHS Research Ethics Committee (20/LO/0598)

3.5 Trial indemnity

University of York will provide indemnity and compensation in the event of a claim by, or on behalf of participants, for negligent harm as a result of the management of the trial.

University of York will also provide indemnity and compensation in the event of a claim by, or on behalf of participants for negligent harm as a result of the trial design.

Indemnity for medical malpractice, public and products liability will be met by practitioners' own professional insurance.

Indemnity covering activities of staff in primary care practices will be standard NHS indemnity arrangements.

Public liability insurance for study assessments will be provided by the study centre: the Northern College of Acupuncture.

3.6 Dissemination of results

The results of the study will be disseminated via:

- Peer-reviewed scientific journals;
- Internal reports to funding organisations;
- Conference presentations;
- Website publications, including Sante-AF's own website;
- Non-peer-reviewed journals;
- Presentations to patient support groups.

4 Background

Atrial fibrillation (AF) is a common cardiac rhythm disturbance (January et al., 2014), associated with increased risk of stroke (Medi, Hankey and Freedman, 2010; Marini et al., 2005; Kannel et al., 1998). In the UK, AF[1] is defined as one of three types:

- paroxysmal (episodic, less than 48 hours' duration with no treatment);
- persistent (episodes that last for longer than 7 days); or
- permanent (continuous and unremitting) (National Institute for Health and Care Excellence, 2014b).

Risk factors for AF include age, lifestyle choices (including smoking, physical inactivity and nutrition) and current comorbidities (Nalliah, Sanders and Kalman, 2018; Benjamin et al., 2017; LaMori et al., 2012). With an ageing population and the increasing adoption of unhealthy lifestyle choices, prevalence stands at its highest ever in the developed world, and incidence is increasing (Schnabel et al., 2015; Chugh et al., 2014; Krijthe et al., 2013). In the UK, the estimate of AF burden is 2.5% of the population or 1.4 million people (Public Health England, 2015). The cost of AF treatment, including hospital admissions, outpatient consultations, general practice consultations and drug treatment, was estimated to cost £459 million or 0.97% of total NHS expenditure in 2000 (Stewart et al., 2004).

Current treatment strategies for AF focus on "prevent[ing] complications, particularly stroke, and alleviat[ing] symptoms" (National Institute for Health and Care Excellence, 2014b:5). The presence of one or more stroke risk factors in addition to AF indicates the need for anticoagulation therapy (ibid.:89), while the alleviation of symptoms focuses on the restoration of normal heart rhythm (known as cardioversion). First-line strategies, focused on rate and rhythm control, are pharmacologic; if unsuccessful, patients progress to electrical cardioversion (a controlled shock to the heart to restore normal rhythm) or catheter ablation (a minimally-invasive procedure by which a catheter removes the heart tissue thought to cause the arrhythmia) (ibid.:263). A rare option is surgical ablation, which is carried out during surgery (Kirchhof et al., 2016).

However, many strategies do not achieve cardioversion, and some have the added disadvantage of promoting arrhythmic propensity (Packer et al., 2018; Al-Khatib et al., 2014) and the risk of non-

[1] That is, 'valvular' AF unrelated to dysfunction of the heart valves such as that associated with rheumatic mitral stenosis

cardiac and all-cause mortality (Pandya et al., 2016). Recurrent and refractory AF are treated by repeated cycles of the above care pathway; however, repetition is associated with increased risk (Freeman et al., 2018; Shah et al., 2012). Adverse effects of treatment affect quality of life for some patients (Zhuo et al., 2020; Aliot et al., 2014). Moreover, all strategies demonstrate a long-term inability to maintain rhythm (Lau et al., 2017; Vitali et al., 2018). One systematic review concluded that "…rate and rhythm control strategies have [no significant effect] on major clinical outcomes" (Caldeira, David and Sampaio, 2011:226-7). Vizzardi and colleagues (2014) noted the incidence of atrial fibrillation recurrence within three months following pharmacological/electrical cardioversion as 40-50%.

As treatment increasingly does not aim at a permanent cure for AF, recent research has focused on quality of life for AF patients (Walters et al., 2019; Witassek et al., 2019; Son et al., 2019; Jankowska-Polanska et al., 2018; Tan et al., 2018; Vimalesvaran, Dockrill and Gorog, 2018) and particularly on the quality of life associated with various interventions (Miura et al., 2020; Blomström-Lundqvist et al., 2019; Joensen et al., 2019; Mark et al., 2019; Driessen et al., 2018; Malm et al., 2018). A recent integrative review demonstrated that health-related quality of life in AF patients was driven by factors including AF-specific anxiety, and frequency/severity of symptoms (Son et al., 2019).

A small body of evidence suggests that traditional acupuncture and nutritional therapy may affect AF symptoms and general quality of life. Further research is warranted.

4.1 The relationship between AF symptoms and quality of life

For people with atrial fibrillation, symptom levels appear to be related to quality of life in inverse ratio: the higher the level of symptoms, the lower the quality of life (Son et al., 2019); interventions may also affect quality of life independently of symptom level, or vice versa. Hypotheses for a future trial (Section 3.4.1) are therefore expressed individually in relation to each outcome; a future trial will evaluate each individual outcome as a result of the intervention, and will also investigate strength and direction of the relationship between the individual outcomes.

4.2 Current evidence for Acupuncture and Nutritional Therapy

4.2.1 Acupuncture for AF symptoms

Isolated case studies and some small trials of acupuncture for cardiac arrhythmias were published 1973-2003, but all are of poor methodological and reporting quality. More recently, two case studies

(a 62-year-old male and a 72-year-old female) showed spontaneous conversion to sinus rhythm following traditional acupuncture (Jonkman and Jonkman-Buidin, 2013; Valaskatgis et al., 2008). In 2011, a small-scale randomised controlled trial of 80 patients after electrical cardioversion found that traditional acupuncture was associated with a recurrence rate comparable to the anti-arrhythmic drug amiodarone, and was superior to sham acupuncture or no treatment (Lomuscio et al., 2011). However, all evidence appears to be of low quality and does not robustly confirm the effect of acupuncture on AF symptoms; further research is needed.

4.2.2 Acupuncture for AF-related quality of life

There is no current evidence demonstrating the effect of acupuncture on quality of life specifically related to AF; however, robust evidence exists to demonstrate a positive effect of acupuncture on quality of life related a variety of conditions that are associated with AF as comorbidities, including complications of diabetes and vascular disease (Meyer-Hamme et al., 2018); stroke sequelae (Zhang et al., 2018); and heart failure (Ni and Frishman, 2018). Further research is needed to evaluate the effect of acupuncture on quality of life for AF patients.

4.2.3 Nutritional Therapy for AF symptoms

A range of cohort and case-control studies indicate that adherence to Mediterranean diet (Mattioli et al., 2011), increased caffeine (Mostofsky et al., 2015) and decreased alcohol intake (Larsson, Drca and Wolk, 2014), Omega-3 polyunsaturated fatty acids (Martino et al., 2016), and weight loss (Eckel et al., 2014) are associated with reduced AF symptoms. (Note that the Mediterranean diet may be contraindicated for anticoagulated patients; see Section 4.9.3 and the National Institute for Health and Care Excellence's Clinical Knowledge Summary on anticoagulation (2020).

While these studies are of high quality, they indicate single dietary strategies rather than the approach of the nutritional therapist, which is to combine therapeutic strategies in an overall dietary plan individualised to the specific needs of each patient. Further research is needed to investigate this approach in relation to AF symptoms.

4.2.4 Nutritional therapy for AF-related quality of life

The evidence-base for nutritional therapy is slight, and no current evidence has been found demonstrating the effect of nutritional therapy on general or AF-related quality of life. However, one recent study showed that patients with early persistent AF associated with heart failure who received, alongside pharmacological therapies, counselling for dietary restrictions, alcohol use,

sodium restriction and caffeine use, registered an improved quality of life (De With et al., 2019). In addition, some specific dietary interventions that are independently associated with a reduction in AF symptoms (see Nutritional Therapy for AF symptoms) have also been independently associated with improved health-related quality of life, namely the Mediterranean diet (Galilea-Zabalza et al., 2018; Govindaraju et al., 2018); reduced alcohol intake (Yao et al., 2019); and weight loss (Kolotkin and Andersen, 2017). (Note that the Mediterranean diet may be contraindicated for anticoagulated patients; see Section 4.9.3 and the National Institute for Health and Care Excellence's Clinical Knowledge Summary on anticoagulation (2020)). Note that the approach of a nutritional therapist is to combine therapeutic strategies rather than prescribe a single diet or dietary intervention. Further research is needed to investigate the effect of this approach on quality of life for AF patients.

4.3 Current evidence for lifestyle modification

Recent European guidelines for the management of AF (Kirchhof et al., 2016) indicate that lifestyle modification may be an important component of the effect of treatment (Abdul-Aziz et al., 2018; Di Benedetto et al., 2018; Hong and Glover, 2018; Malmo and Nes, 2016; Mohanty et al., 2014). As patient-specific lifestyle change and behavioural support are important components of both acupuncture and nutritional therapy (Celis-Morales et al., 2017; MacPherson et al., 2017), it is premised that – in addition to reducing symptoms and/or achieving cardioversion – both therapies may promote longer-term AF-free survival with the offer of lifestyle advice and support for behaviour change. No research has been identified that investigates this hypothesis in relation to these therapies.

4.4 Research question for a future trial

In a future larger-scale randomised controlled trial, it is proposed to test the effect of these two interventions when used adjunctively to usual care, seeking to answer the research question "What is the effect of acupuncture or nutritional therapy in addition to usual care on quality of life and symptoms in persons with atrial fibrillation?".

4.4.1 Hypotheses for a future trial

The hypotheses for a future randomised controlled trial are:

H1: Acupuncture or nutritional therapy in addition to usual care has an effect on quality of life in persons with atrial fibrillation.

H2: Acupuncture or nutritional therapy in addition to usual care has an effect on symptoms in persons with atrial fibrillation.

H0: Acupuncture or nutritional therapy in addition to usual care has no effect on quality of life or symptoms in persons with atrial fibrillation.

4.5 Rationale for the feasibility study

There are several areas of uncertainty associated with a future larger-scale trial. This feasibility study will address the most significant of these.

4.6 Research question for the feasibility study

Is it feasible to conduct a future large-scale randomised controlled trial to evaluate the effect of acupuncture and nutritional therapy in addition to usual care on quality of life and symptoms in persons with atrial fibrillation?

4.6.1 Hypotheses for the feasibility study

The hypotheses for this feasibility study are:

H1: It is feasible to conduct a future randomised controlled trial to evaluate the effect of acupuncture and nutritional therapy in addition to usual care on quality of life and symptoms in persons with atrial fibrillation.

H0: It is not feasible to conduct a future randomised controlled trial to evaluate the effect of acupuncture and nutritional therapy in addition to usual care on quality of life and symptoms in persons with atrial fibrillation.

4.7 Aim and objectives for the feasibility study

4.7.1 Aim

To test the feasibility of several aspects of a future trial's design.

4.7.2 Objectives

(1) To evaluate participants' **willingness to be randomised**;

(2) To evaluate **appropriateness of eligibility criteria** (including practitioner eligibility);

(3) To evaluate participant **retention**;

(4) To evaluate acceptability of **interventions**;

(5) To evaluate acceptability of participant **assessments**;

(6) To evaluate the **effect** of ambulatory ECG devices (AEDs);

(7) To explore **participant experience** of study participation, for practitioners and participants;

(8) To evaluate the **feasibility** of all the above objectives during a pandemic.

5 Methods

5.1 Description of feasibility study design

This feasibility study is undertaken to inform a pragmatic three-arm parallel trial comparing:

- Usual care + acupuncture (Group A);
- Usual care + nutritional therapy (Group B);
- Usual care alone (Group C).

The study takes a pragmatic approach, meaning practitioners will work within their usual scope of practice (rather than following a standardised protocol).

5.1.1 Research approach of the feasibility study

The feasibility study takes a mixed methods approach. Quantitative methods are used to investigate to what extent a given aspect of the trial is feasible, while qualitative methods aim to explore reasons for the level of feasibility.

5.1.1.1 Ontological and epistemological paradigms of the study's qualitative methods

As the qualitative study is nested within a pragmatic trial, it is appropriate to adopt a constructivist-pragmatic approach; in exploring the nature of participants' realities regarding AF, trial participation and their experience of their therapy, the study is essentially phenomenological in character and will focus on "data… useful for stakeholders" (Mertens and Wilson, 2019:37; Song, Sandelowski and Happ, 2015). Accordingly, from an epistemological perspective the study will regard knowledge as generated by participants' subjective experience (Ritchie et al., 2013), and will acknowledge the multiplicity of participants' realities by representatively reporting the various perspectives that emerge thematically during a reflective inductive analysis process (Creswell and Poth, 2018). Non-conforming cases and sub-themes will also be discussed.

Axiologically, the researcher's positionality as a qualified acupuncturist will be made explicit to participants. The study will include critical consideration of positionality, including gender, experience and investment in the research (Creswell and Plano Clark, 2018).

5.2 Patient and public involvement (PPI)

A panel of two patients with AF and one lay member of the public was convened to advise on the following:

- Outcomes likely to be of significance to patients with AF;
- Development of measurement instruments, including the Interview Topic Guides, which were piloted with both patient members of the panel;
- Participant burden;
- Overall participant dignity, privacy, confidentiality and study-related wellbeing.

The PPI panel met twice: once at the start of study design, and once before the end of study design; the lay member commented on study documentation by correspondence. Each meeting lasted for approximately one hour, and resulted in changes to study design and documentation.

All members of the panel have contributed to the design and wording of the participant-facing documentation, and have made various amendments to ensure clarity. The two AF patients in particular offered views on:

- The nature of the interventions as potentially offering reduced risks and greater acceptability than current usual care;
- The requirement for the study and its practitioners to emphasise the need for participants to maintain their existing usual care regime, despite any change in symptoms as a result of receiving treatments in the study.

No members of the PPI panel will have direct contact with study participants, or direct involvement as researchers or data analysers. No PPI panel member will be party to confidential information at any stage.

5.3 Eligibility criteria

There are two types of participant in the feasibility study:

1. Practitioners of acupuncture and nutritional therapy ("practitioners");
2. AF patients ("participants").

Eligibility criteria have been defined for both types of participant (Eligibility criteria for participants; Eligibility criteria for practitioners).

There is no eligibility stipulation as to gender, race/ethnicity, social condition, sexual preference or faith.

5.3.1 Eligibility criteria for participants

Participant eligibility criteria are listed in Table 1 and Table 2, below.

Table 1: Participant inclusion criteria

	Inclusion criterion	Justification	Checked by GP surgery before initial contact?	Question # in screening phone call by researcher
1	Aged ⩾ 45 and ⩽70	Age range with greatest prevalence of AF and optimum ability to apply lifestyle advice	Yes	1
2	Diagnosis of AF ⩾ 6 months and ⩽ 60 months previously	To coincide with a hypothesised 'settling in' post-diagnosis period in which conventional treatment has become stable	Yes	3
3	Stroke prevention measures offered/applied where indicated	To reduce risk of stroke (National Institute for Health and Care Excellence, 2014a)	Yes	n/a
4	(Self-detectable) paroxysmal atrial fibrillation (of at least weekly frequency)	Necessary to reliably complete 7-day self-report diary	AF status checked by GP but detectability, paroxysmal status and frequency checked in screening phonecall	4, 5, 6
5	Owner of, and able to use, a mobile phone	For study communication and compliance prompting	No – explicitly consented in Consent Form (& checked in screening phone call)	20
6	Home broadband of sufficient capacity to sustain NT appointments and study assessments	For Nutritional Therapy appointments (if allocated to this group) and online study assessments	No – explicitly consented in Consent Form (& checked in screening phone call)	21
7	Owner of, and able to use, a device equipped with Microsoft Teams video-calling software OR happy to use study iPad	For online study assessments	No – explicitly consented in Consent Form (& checked in screening phone call)	22
8	Willing to have acupuncture or nutritional therapy alongside usual care, or usual care alone	To comply with study requirements	No – explicitly consented in Consent Form	No – explicitly consented in Consent Form
9	Willing to travel to attend appointments for acupuncture *(travel expenses are subsidised)*	To attend acupuncture appointments if allocated to that group	No – explicitly consented in Consent Form	No – explicitly consented in Consent Form
10	Willing to wear a CardioSTAT® ambulatory ECG device (AED) for 7 days x 2 times over the course of approximately three months, then return in reply-paid envelope to the manufacturer for data analysis	To provide AF monitoring data	No – explicitly consented in Consent Form	No – explicitly consented in Consent Form
11	Speak/understand English well enough to engage meaningfully with interventions and assessments (note this is researcher's judgement)	The study does not have a budget to provide translation/other assessment support	No – researcher's judgement during phone call to ascertain eligibility	Questionnaire contains a prompt (Q19) to researcher to make a judgement
12	Able to give informed consent	To comply with ethical requirements	Yes	No – explicitly consented in Consent Form

Table 2: Participant exclusion criteria

	Exclusion criterion	Justification	Checked by GP surgery before initial contact?	Question # in screening phone call by researcher
1	Diagnosed with valvular AF	AF is not amenable to study interventions	Yes	n/a
2	Pacemaker, implantable defibrillator, neurostimulator, any other type of active implantable device	Avoidable confounding factor, plus contraindicated to CardioSTAT®	Yes	n/a
3	Diagnosed with kidney disease levels 4 or 5	Contraindicated to nutritional therapy	Yes	n/a
4	Diagnosed with terminal or severe illness	Participant unlikely to engage with treatments or apply lifestyle advice	Yes	n/a
5	Diagnosed with any blood clotting disorder * Note that working with *anticoagulated* patients is within normal scope of practice for acupuncturists and nutritional therapists; see A note on acupuncture and anticoagulation medication and Harms and adverse effects of nutritional therapy	Contraindicated to acupuncture	Yes	n/a
6	Diagnosed (including self-diagnosis) with any condition or disorder contraindicating suitable moderate exercise	Contraindicated to exercise	Yes, but also checked in screening phonecall	7
7	Diagnosed (including self-diagnosis) with any eating disorder past or present	Contraindicated to nutritional therapy	Yes, but also checked in screening phonecall	8
8	Pregnant or trying to conceive	For safety of pregnancy	Yes, but also checked in screening phonecall	9
9	Currently taking part in other research rendering participant unable to have either intervention, or which is likely to affect study outcomes, or which renders it unsafe for participant to continue	For protection of participant and integrity of study	Yes, but also checked in screening phonecall	10
10	Currently having, or have had in the last six months, a course of acupuncture or nutritional therapy	To protect integrity of study	No – checked in screening phonecall	11
11	Classified as shielding, clinically vulnerable or clinically extremely vulnerable with regard to COVID-19, or living with or bubbled with anyone in any of these categories (https://www.nhs.uk/conditions/coronavirus-covid-19/people-at-higher-risk/whos-at-higher-risk-from-coronavirus/)	To protect participant and household against increased risk of cross-infection with COVID-19	Yes, but also checked in screening phonecall (GP not necessarily aware of living/bubbling arrangements)	12-16
12	Regularly using a TENS machine or receiving any kind of energy delivery	Contraindicated to CardioSTAT®	Yes, but also checked in	17

	therapy to the upper torso (diathermy therapy, diagnostic or therapeutic ultrasound, radiation therapy, electro-surgery or x-ray)		screening phonecall	
13	Any other clinical reason why patient should be excluded, in the clinical judgement of the patient's GP	To protect patients	Yes	n/a

5.3.2 Eligibility criteria for practitioners

Practitioner eligibility criteria are listed in Table 3 and Table 4, below.

Table 3: Practitioner inclusion criteria

	Inclusion criterion	Justification
1	Qualified to minimum BSc level in either therapy	To assure quality of interventions and congruence with practising base of therapists
2	Minimum of three years' post-qualification experience in continuous active practice	To assure quality of interventions
3	Full member of the relevant professional body (British Acupuncture Council or British Association of Nutritional Therapy and Lifestyle Medicine)	To assure a level of professional and ethical conduct; to maintain insurance in case of post-treatment claims
4	Full professional insurance, and undertaking to maintain such insurance for a minimum of one year after the end of active involvement with the study	To provide intervention-related indemnity
5	Possessed of any necessary local regulatory permits	To ensure interventions are within scope of applicable byelaws
6	(Acupuncturists only) Operating with a current waste disposal contract including the provision of Duty of Care notices for contaminated sharps disposal	To ensure intervention is within scope of applicable law
7	Willing and able to engage with study procedures and parameters of practice, including training (as set out in Practitioner eligibility questionnaire)	To meet study requirements
8	[Acupuncturists only] Premises within five-mile radius of York city centre	To minimise travel burden for participants
9	[Acupuncturists only] Willing to abide by the COVID-19 practice guidelines set out by the British Acupuncture Council	To maintain COVID-19-related safety for participants
10	[Nutritional Therapists only] Willing and able to hold all consultations and participant contact by online methods only	To maintain COVID-19-related safety for participants

Table 4: Practitioner exclusion criteria

	Exclusion criterion	Justification
1	Any unresolved fitness-to-practise, professional conduct, legal, ethical or disciplinary issues	To avoid bringing the study into disrepute

5.4 Recruitment, consent and retention

5.4.1 Participant recruitment and consent

Stage 1: **Participant identification:** Participants will be identified from medical records held at ~~up to 5~~ local primary care practices in York. Computerised searches will be carried out by the direct care team using database codes to identify participants according to the externally verifiable criteria in Table 1 and Table 2. This will determine the total number of eligible patients according to GP records.

A medically qualified member of staff will scrutinise the patient's medical records to determine the presence of any further exclusion criteria held on the patient's medical record (see Table 2, above: criteria 1-9 and 11-13).

A direct care team member will sign/date the introductory letter, then address and send a Permission to Approach pack to all patients meeting the criteria. The information pack will comprise:

- An introductory letter;
- A Basic Study Information Sheet;
- A Permission to Approach form;
- An addressed, stamped return envelope.

Stage 2: **Informed consent:** The Permission to Approach form is returned by the patient direct to the researcher at the Northern College of Acupuncture (the study centre). On receipt, the researcher will send the patient:

- A covering letter;
- A Participant Information Sheet;
- Two copies of a Consent Form;
- A stamped addressed envelope for return of one copy of the Consent form.

The researcher will call the patient to offer the opportunity to discuss the study and answer any questions before consent is given.

Stage 3: **Eligibility check and initial data collection:** On receipt of a signed Consent Form, the researcher will carry out a screening phonecall with the patient to determine full eligibility on the basis of self-report, according to the criteria in Table 1 and Table 2. Participants will be asked about their availability for treatment, and asked to declare any periods of non-availability known at this stage. This information will be used with the equivalent information derived from practitioners (see Practitioner recruitment) to match participants with practitioners to expedite treatment.

Extra questions will also be asked of those participants indicating willingness to be interviewed for the qualitative arm of the study, allowing the researcher to judge the participant's ability to communicate coherently, expressively and reflectively (Bernard, 2018; Creswell and Plano Clark, 2018). This will contribute to the decision on whether to include the participant in the qualitative arm's purposive sample (see Stage 4 below). Information gathered will be incorporated in the qualitative data analysis.

Patients who are contraindicated to participate by the screening phonecall, and those who respond after the study has been populated, will be notified by letter.

Stage 4: **Randomisation and baseline assessment:** Patients confirmed eligible will be notified by letter and an online baseline assessment will be arranged. The baseline assessment comprises:

- The measures set out in the Study Assessment Table (Table 6, below);
- the fitting of a CardioSTAT® AED if the participant has been randomly selected for this;
- an interview if the participant has been purposively selected for interview (see Sampling strategy for participant interviews).

Participants will be supplied with equipment and guided to carry out all activities during an online video call with the researcher.

All participants will be asked to complete a 7-day self-report AF symptom diary and return this to NCA in a stamped addressed envelope. Participants randomised to wear a CardioSTAT® AED will return these to the manufacturer after 7 days for data analysis.

Note that randomisation takes place immediately before the baseline assessment is carried out, but allocation will not be revealed until after assessment (i.e., involving a short deception of participants). It is necessary to randomise at this stage because:

- Only 33% of each group receives an AED, randomly allocated within that group;
- These are fitted at baseline assessment to avoid undue burden on participants associated with repeat online sessions;
- Distribution of AEDs should be proportionately equal across groups.

Therefore it is necessary to know the participant's group allocation before they can be randomised to receive an AED.

On close of recruitment period, the researcher will receive a completed GP IT Record Search from each participating primary care practice. Data from this will be used to answer Objective 2, in conjunction with the data from the screening phone call.

Stage 5:

Notification of allocation: Once all baseline data has been received for a participant, a letter will be sent to inform the participant of group allocation. If allocated to an active intervention group, the letter will contain details of the practitioner to whom the participant has been allocated. Participants will be encouraged to contact the practitioner to arrange a first appointment. Participants unhappy with their allocated practitioner are encouraged to contact the researcher for re-allocation before their first appointment.

An SMS poll will be conducted to determine the participants' level of satisfaction with treatment allocation, and level of expectation of treatment.

The recruitment period will remain open until the target number of participants has been recruited. Once the study is fully enrolled, all unused Permission to Approach packs will be retrieved from primary care practices. These will be used to produce ratios of participants approached to participants enrolled, to help answer Objective (1) (participants' willingness to be randomised).

5.4.2 Practitioner recruitment and consent

A cross-sectional survey will be undertaken to identify and recruit practitioners. Initial identification will be via the online membership directories of their respective professional associations, which will assure inclusion criteria #3-6 of Table 3; #8 will also be checked. An invitation email will be sent, including a Study Information Sheet inviting the practitioner to complete a questionnaire in which all inclusion and exclusion criteria will be checked. The questionnaire will also be used to ask about availability over the coming months, in order to match available practitioners with participants to expedite delivery of the interventions. Following this, exclusion criterion #1 of Table 4 will be checked with the relevant professional association. Ineligible practitioners will be notified by email. After three weeks (allowing time for practitioners to respond), three eligible practitioners of each therapy will be randomly selected from the total eligible, and these three will be sent letters and contracts for electronic signature. Unsuccessful practitioners will be notified by email. A 'reserve list' of practitioners will be held in case of dropout or other reasons to withdraw practitioners during the study period.

5.4.3 Processes to enhance participant retention

5.4.3.1 Minimising resentful demoralisation for Group C participants

The usual care group (Group C) will be made more attractive to participants by emphasising (i) the benefits of AED monitoring for 33% of each group's participants, and (ii) the important role played by the usual care group participants. Emphasis is given in the patient information sheet and reiterated in the group placement notifications letter.

5.4.3.2 Compliance prompting

Participants will be prompted by SMS message, coordinated centrally by the researcher using an online SMS communications tool (via an NHS Digital DSP Toolkit compliant supplier). Prompts will generally concern the following study flow points:

- Confirmation and reminder of online assessment bookings (for all participants);
- Return of any take-home measures, including 7-day AF diary and CardioSTAT® ambulatory ECG devices.

5.4.3.3 Participant newsletter

A newsletter will be designed and circulated to participants at the approximate halfway point during the intervention period, containing a mix of study news and items of interest to AF patients.

5.4.3.4 Incentive to return final follow-up data

Participants who complete all assessments will receive a £10 retail voucher. This is intended to:

- Minimise loss to follow-up and maximise number of complete participant datasets gathered;
- Motivate participants without disproportionate inducement.

5.5 Randomisation

Methods of randomisation for the feasibility study are described below.

5.5.1 Methods used to generate and conceal the random allocation sequence

Note that a future trial will use its own methods of randomisation; therefore, methods of randomisation in the feasibility study need not be indicative of those used in a future trial.

Using the Simple + blocked randomisation list creation facility at the website www.sealedenvelope.com (Sealed Envelope, 2020), a randomly permuted blocked allocation sequence will be generated using a 2:2:1 ratio, random block sizes of 5 and 10, and a list length of 30. Randomisations will take place at the time of each participant's baseline assessment. Each participant's allocation will be emailed to the researcher and stored in the study's data repository for future reference.

A further simple randomisation list will be created in Microsoft Excel to randomise the participants in each group who will be asked to wear a CardioSTAT® ambulatory ECG device (AED).

Participants willing to be interviewed will be stratified according to the maximal variation sampling strategy across four variables of age, gender, length of diagnosis and previous experience of complementary therapies.

5.5.1.1 Concealing the random allocation sequence

Note that the researcher is not blinded to group allocation, or AED allocation. This is not possible in this trial, which has a single researcher and assessor (KC). This will be critically discussed in the thesis.

- Before booking each participant's online baseline assessment, the researcher will randomise the participant using the facility at sealedenvelope.com. This will randomise the participant to a group and will email the allocation, keyed to the participant's Study ID number, to the researcher. The researcher is therefore blinded to the group allocation sequence and will be unable to predict this, although she will not be blinded to the group allocation itself.
- It is necessary to randomise the participant before the baseline assessment, because
  - only 33% of each group will be randomised to wear the CardioSTAT® AED;
  - the AEDs are fitted at the baseline assessment to avoid further participant burden with repeated online sessions.

  It is therefore necessary to know the participant's group allocation before the baseline assessment, in order that the appropriate number of participants within each group can be randomly selected to wear an AED.
- The researcher will mark the sequential enrolment number and Study ID number in the next available cell in the appropriate group column of the spreadsheet containing the randomised allocation of AEDs. This will allow the AEDs to be randomly allocated within the group.
- Group allocation will not be revealed to the participant until after the baseline assessment data has been fully collected (i.e., once the 7-day

symptom diary and AED as applicable have been received by the researcher). This is to prevent any contamination of expected treatment effect or resentful demoralisation before the baseline assessment is carried out.

5.5.2 Enrolment

A letter will be sent to each participant randomised, to inform them of group allocation. The letters will also contain details of the practitioner to whom the participant has been allocated, and participants will be encouraged to call the practitioner to arrange a first appointment. Participants who do not wish to attend their allocated practitioner will be offered an alternative practitioner before their first appointment.

SMS reminders will be sent after 1 and 2 weeks, followed by a letter. Participants who do not arrange a first appointment within four weeks of study commencement will be treated as lost to follow-up, and will be invited by letter to share any reasons for not commencing treatment/ consultations.

The participant's GP will be notified of allocation by letter and copies of the Participant Information Sheet and signed Consent Form will be provided for the patient's medical record.

5.6 Interventions

Both acupuncture and nutritional therapy are premised on an understanding of the patient as a complex and unique individual, whose overall health is influenced by not only physical but also mental, emotional and spiritual factors (BANT, 2018, 2015; Eckersley et al., 2009). A wide range of information is collected at the first appointment, including personal history and medical history, living circumstances and lifestyle choices in addition to physical health signs and symptoms; this is used in both therapies as the basis for a highly individualised strategy to address health issues.

The therapeutic effect of both interventions may also include:

- lifestyle advice, including dietary advice, and behaviour modification support (Evans et al., 2011);
- the patient/practitioner relationship (Prady et al., 2013).

This study will be a pragmatic study in which interventions are not standardised but are instead delivered within the scope of practice in which the practitioner is trained and qualified. A description of this scope of practice is given below for each intervention.

5.6.1 Acupuncture: description of scope of practice

Traditional acupuncture is based on ancient principles of Oriental medicine. Treatment effects are achieved via the stimulation of acupuncture 'points' on channels or 'meridians' in the body, which provokes modulation of sympathetic tone and motor reflexes, endogenous descending pain inhibitory and facilitatory systems, activation or de-activation of limbic structures, HPA axis, prefrontal and frontal cortices, parasympathetic activity and immune system activation amongst others (Lund and Lundeberg, 2016; Cheng, 2014; Kawakita and Okada, 2014).

In order to ensure best practice, all acupuncture treatments given as part of the Santé-AF study will be delivered within the scope set out in the Acupuncture Study Manual. This document has been developed by consensus with the Acupuncture Therapy Advisory Panel (see Study personnel).

5.6.1.1 Acupuncture treatment: what happens

A first acupuncture appointment is typically around 90 minutes long and includes a consultation period in which a full range of information is gathered on the patient's presenting conditions, medical and other types of history, diet and lifestyle. Following this, an initial diagnosis made according to the principles of TCM, and a treatment based on the diagnosis is carried out. Following this, repeat treatments are usually around an hour's duration and comprise a consultation period in which progress is discussed, treatment strategy is adjusted as necessary, and the treatment is carried out.

5.6.1.2 Acupuncture: length of treatment

For the purposes of this study, the acupuncture intervention will comprise up to eight treatments delivered at a frequency determined by the practitioner and the participant over a period up to 12 weeks. Participants will be encouraged to take eight once-weekly treatments over an eight-week period if possible.

5.6.2 Nutritional therapy: description of scope of practice

Nutritional therapy (NT) consists in the application of nutrition science to promote health. The initial consultation gathers information from the client on signs and symptoms potentially indicating factors such as compromised gut function, environmental factors, hormone and neurotransmitter regulation, detoxification and energy production/oxidative stress. Based on the initial consultation information, a highly individualised dietary strategy is drawn up to support nutritional balance and thereby promote health (BANT, 2015).

In order to ensure best practice, all Nutritional Therapy treatments given as part of the Santé-AF study will be delivered within the scope set out in the Nutritional Therapy Study Manual. This document has been developed by consensus with the Nutritional Therapy Advisory Panel (see Study personnel).

5.6.2.1 Nutritional Therapy consultation: what happens

A first NT appointment is usually 90 minutes to two hours in duration, during which a range of detailed information is gathered on the patient's presenting conditions, diet, lifestyle, and medical and other types of history. Brief nutritional advice may be given at this first appointment. Following this, a detailed dietary analysis and strategy is formulated and the patient returns for a second appointment to discuss this (around an hour). Following this, the patient begins to implement the strategy, and returns for a follow-up appointment (about an hour) some weeks later to check progress and adjust the strategy as required.

5.6.2.2 Nutritional Therapy: length of course of consultations

For the purposes of this study, the NT intervention will comprise up to three consultations delivered at a frequency determined by the practitioner and the participant over a period up to 12 weeks. In this study, all consultations will be held online to minimise the risk of cross-infection with Covid-19.

5.6.3 Usual care

For the purposes of this feasibility study, usual care comprises the care pathway as defined by the NICE guideline on atrial fibrillation (National Institute for Health and Care Excellence, 2014a) and

delivered via primary care practices in conjunction with hospital consultants and/or other healthcare professionals.

5.6.4 The Therapy Advisory Panels

Two Therapy Advisory Panels (TAPs) were convened to inform this feasibility study, comprising senior acupuncturists and nutritional therapists (see Study personnel for details). The TAPs are responsible for advising on the following study elements:

- ascertaining clinically contraindicated practice in each therapy for AF patients and drawing this up into two therapy-specific Study Manuals to which study practitioners are contractually obliged to adhere;
- helping to define adverse events related to the therapies;
- supporting safety, best practice and ethical compliance within each therapy's codes of professional conduct.

5.6.5 Study Manuals

Two Study Manuals were developed for the use of practitioners in the study. Along with trial processes, these define the scope of practice for treating AF patients within the study and set out any contraindicated components of treatment/dietary advice.

Practitioners will be contacted regularly throughout the intervention period of the study, to ascertain and reinforce compliance with the scope of treatment/consultation set out in the Study Manuals. This will form part of the process of monitoring adverse events (see Section 4.9).

5.6.6 Reporting interventions

All treatments/consultations for each intervention will be reported using two log books designed and tested by the Therapy Advisory Panels.

5.6.6.1 Acupuncture log book

- Participant's TCM diagnosis and treatment strategy adopted;
- Components of each treatment, with rationale;
- Treatment parameters;

- Lifestyle advice given, and rationale for this;
- Participant's reported level of compliance with lifestyle advice, followed up at each appointment;
- Adherence to appointment schedule;
- Any adverse events;
- All COVID-19 precautions taken.

5.6.6.2 NT log book

- Full report of intake consultation/information;
- Participant's dietary analysis and strategy, with rationale;
- Lifestyle advice given, and rationale for this;
- Any adjustments to the strategy, with rationale;
- Participant's level of compliance with lifestyle advice, followed up at each consultation;
- Adherence to appointment schedule;
- Any adverse events.

5.6.6.3 Checking compliance with scope of treatment/consultation

All practitioners' returned Log Books will be checked to ensure compliance with the scope of treatment/consultation as set out in the respective Study Manuals.

5.7 Training practitioners

A training event will be held for all practitioners, to familiarise them with study procedures. Issues covered will include:

- Study procedures, including reporting using the log books;
- [for acupuncturists only] Compliance with Covid-19 safety during treatments;
- Study safety, including Emergency Care Plans, any necessary aftercare advice, the Therapy Guidelines (including therapy-specific issues in working with AF) and

reporting of adverse events using the NIHR Safety Reporting Flowchart (National Institute for Health Research, 2016);

- Participant confidentiality, anonymity and pseudonymisation procedures during the study;
- Refreshing of practitioner training in lifestyle advice and behaviour change support;
- The requirement for ongoing consent at each treatment/consultation.

5.8 Safety of study interventions

In general, the potential for harm or adverse events caused by the study's interventions is judged to be low compared with the safety record of conventional treatments for atrial fibrillation. The evidence for this is set out in the following sections.

5.8.1 Adverse events

An adverse event is defined as "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" (NIHR, 2011).

Practitioners' professional training and membership of their professional body equip them to recognise and handle adverse events relating to their therapy ("adverse reactions"). Training will be given to help practitioners recognise and report adverse events that are not related to their therapy ("serious adverse events" and "adverse events unconnected with treatment").

Table 5 below sets out the different types of adverse event in relation to the Santé-AF study, together with the action required. In addition, practitioners will mark any adverse events in the Log Book for that participant, with a brief description of the event.

Table 5: Adverse event definitions, and actions required

Type of adverse event	Definition	Action required
Serious adverse event (SAE) Report immediately to the researcher by phone	Any event that: • Results in death • Is, or results in, a life-threatening situation (note that this includes COVID-19 infection) • Requires hospitalisation or prolongation of hospitalisation • Results in persistent or significant disability or incapacity • Consists of a congenital abnormality or birth defect	If the SAE can POSSIBLY be attributed to the intervention received, the practitioner will inform the researcher immediately by telephone using the *Items to Report when Reporting Adverse Events* list in the practitioner's Study Manual. The researcher will inform the Chief Investigator (JW), who will report to the NHS Research Ethics Committee within 15 days. The researcher will inform the sponsor representative (MB) of reports made to the NHS REC. The NHS REC will require a decision regarding withdrawal from the study to be made by the Chief Investigator (CI), taking into account necessary advice available to the CI from the Trial Steering Committee and the University of York Health Sciences Research Governance Committee. If the SAE can definitely NOT be attributed to the intervention received (for instance, if it happens after study enrolment but before any interventions have been received), the Trial Steering Committee will be informed and advice provided.
Adverse reaction (AR) Report to the researcher by email	Any event that: • Is NOT expected to occur in normal clinical practice, and which is of concern to the practitioner or their patient, but is less serious than the Serious Adverse Events above. ARs are defined for each intervention in the Study Manual for that intervention. For instance, in acupuncture, bruising may be an AR; in nutritional therapy, constipation may be an AR.	**Any** AR should be reported to the researcher by email using the Items to Report when Reporting Adverse Events list in this Manual. The researcher will refer to the Trial Steering Committee for further advice. Practitioners will ensure that the participant is safe and as well as possible – for instance, an emergency contact may be activated, and subsequent follow-up should be made to ensure no long-lasting effects have been experienced. The AR should then be discussed by the practitioner with the individual participant and the researcher, and a joint decision taken regarding the participant's continuation in the study.
Adverse event unconnected with the study treatment (AEU) Report to the researcher by email	Any event that: • Happens during an appointment and is definitely unconnected with the therapy but may be the practitioner's liability. For instance, if the participant injures themselves while on the premises.	**Any** AEU should ALWAYS be reported to the researcher by email using the Items to Report when Reporting Adverse Events list in this Manual. The researcher will report onwards to the Trial Steering Committee. Practitioners must ensure that the participant is safe and as well as possible – for instance, an emergency contact may be activated, and subsequent follow-up should be made to ensure no long-lasting effects have been experienced. In addition to reporting to the researcher, mark the appropriate box in the Log Book, and write a brief description of the event. Adapted from the NIHR Decision Tree for Adverse Events Reporting (National Institute for Health Research, 2016)

In addition to the required reporting set out above, practitioners will be contacted by the researcher on a regular basis throughout the study to determine the occurrence of any adverse events.

All adverse events data will be given in the final study report.

5.8.2 General safe practice of acupuncturists and nutritional therapists

All practitioners in the Santé-AF trial are required to be members of either the British Acupuncture Council (BAcC) or the British Association of Nutritional Therapy and Lifestyle Medicine (BANT). Both memberships are only attainable via undergraduate-level or postgraduate-level degree courses delivered to the core curricula of the British Acupuncture Accreditation Board (BAAB) for acupuncture, or the Nutritional Therapy Education Commission (NTEC) and the Complementary and Natural Healthcare Council (CNHC) for nutritional therapy. Both curricula explicitly set out that:

- practitioners do not offer the therapy as a replacement for medical advice;
- practitioners are trained to recognise 'red flag' symptoms and to refer onwards to the appropriate medical professional (Nutritional Therapy Education Commission (NTEC), 2015; British Acupuncture Accreditation Board, 2011; Complementary and Natural Healthcare Council, 2018)

See Eligibility criteria for practitioners for a full list of eligibility criteria for practitioners recruited to the study.

5.8.2.1 Santé-AF – Covid-19 safety

To minimise the risk of transmission of Covid-19:

- all nutritional therapists will work entirely online, with no face-to-face participant contact at any point;
- all acupuncturists working in the study will follow guidelines on Covid-19-safe practice set out by the British Acupuncture Council. These are wide-ranging and comprehensive, including the following measures:
  - Acupuncturists wear a minimum level of PPE, including impervious aprons and fluid-resistant surgical masks, plus face visors when working within 1 metre of the patient's face;
  - Participants wear masks throughout their appointments, unless lying prone on a treatment couch, at which point they may remove the mask in order to breathe. They are also asked to enter the treatment room without touching

any surfaces, and wash their hands immediately on arrival and again before leaving;

- Full and thorough cleaning is carried out between appointments to ensure that all surfaces contacted by patients or their belongings have been decontaminated;
- Patients are asked to confirm their Covid-19 status immediately before or on arrival at their appointment, and to refrain from attending if they have any symptoms or are self-isolating whilst waiting for test results.

- BAcC members may wish take advantage of the Government's programme of lateral flow testing; practitioners testing positive for Covid-19 must immediately self-isolate and may not treat patients. It is noted that the lateral flow test is not entirely accurate, particularly when self-administered, and in the Santé-AF study BAcC members are required not to make any changes to their Covid-safe practice even if a negative result is obtained from a lateral flow test;
- The Santé-AF Trial Steering Committee (TSC) will monitor levels of Covid-19 in York and will require acupuncturists to stop treating trial participants if levels rise above a pre-determined threshold (see 5.21.2.1 below). Acupuncturists in the study are contractually obliged to stop treating trial participants if required to do so by the TSC;
- BAcC members are classified as key healthcare workers (via the BAcC's status as an accredited register) and at the time of writing (February 2021) may claim priority for vaccinations. While not all BAcC members may choose to have a vaccination, those who do will have a level of protection.

5.8.3 Adverse reactions to acupuncture

Harms or adverse reactions associated with acupuncture are usually "mild and self-correcting"; the most frequent reactions are usually minor bruising around a needle site, and transient dizziness (Melchart et al., 2004; Yamashita and Tsukayama, 2008; Witt et al., 2009; Kawakita and Okada, 2014; Chan et al., 2017).

A recent systematic review on the safety of acupuncture found that, of 167,011 acupuncture treatments delivered for a range of conditions by acupuncturists with a range of training levels, 1.84% resulted in adverse reactions (defined as a spectrum from pneumothorax to local bruising)

and 0.03% in death, concluding that "serious [adverse events] are rare, but need significant attention as mortality can be associated with them. Referrals should consider acupuncturists' training credibility" (Chan, et al., 2017:3369).

A larger study of 229,000 acupuncture patients undergoing 2,338,860 treatments demonstrated 8.6% of patients reporting at least one adverse effect including bleeding or haematoma (6.1% of patients) and pain (1.7% of patients). There were no deaths. The authors concluded that "acupuncture provided by physicians is a relatively safe treatment" (Witt et al., 2009).

The acupuncturists working in the Santé-AF study are members of the British Acupuncture Council (BAcC), and are trained to a minimum BSc/professional Licentiate level. The BAcC Code of Safe Practice sets out a high standard of safety in Chinese medicine diagnosis and treatment, thus minimising the risk of harms or adverse reactions. Nonetheless, on the basis of Chan, et al., it must be concluded that there is a small risk to wellbeing associated with acupuncture treatment.

5.8.3.1 A note on acupuncture and anticoagulation medication

A high proportion of AF patients are likely to be anticoagulated as part of stroke prevention management. Anticoagulated patients are not contraindicated to acupuncture, but cautions are in place with guidelines to minimise the increased risk of bleeding, bruising or compartment syndrome. Consequently, ascertaining anticoagulation status and taking account of this when delivering treatments is within normal scope of practice for all BAcC acupuncturists, including ascertainment of type of anticoagulant medication (including, for warfarin, ascertainment of prothrombin time or international normalised ratio). Strict guidelines are set out by the BAcC regarding type and size of needle, needling technique, and use of supplementary therapies for anticoagulated patients; practitioners are also advised to explain the increased risk of bleeding and bruising to patients. Risk to study participants is mitigated further by the inclusion of refresher training during training workshops held for all study practitioners.

5.8.4 Adverse reactions to nutritional therapy

Adverse reactions to nutritional therapy are not easily defined: there appear to be no published studies that reference nutritional therapy as a discipline in relation to harms or adverse events. It must be concluded that the risk of harm from nutritional therapy is unknown.

Balancing this, the nutritional therapists working in the Sante-AF study are all required to be members of BANT (see above), which requires its members to conduct individualised assessments of risk for each client, in relation to the dietary analysis and strategy provided by the therapist; and which requires all practitioners to demonstrate "understanding and application of… the mechanism of action of common classes of drugs and common drug-nutrient and drug-food interactions" (Complementary and Natural Healthcare Council, 2018:5). Risk to study participants is mitigated further by the inclusion of refresher training during training workshops.

Note that in the Santé-AF study, nutritional therapists are prohibited from:

(i) advising diets incorporating concentrations of foods that may affect the actions of prescribed medications, particularly anticoagulants and specifically Vitamin K antagonists;

(ii) recommending supplements or nutraceuticals.

5.8.5 Participant withdrawal

Participants may withdraw from the study at any time without influencing their future care or treatment. This is set out in the Participant Information Sheet.

The decision to withdraw a participant from the study in view of an adverse event will be taken by the Trial Steering Committee, with appropriate input from the NHS REC and the University of York Health Science Research Governance Committee (see Table 5), and will have immediate effect. The researcher will report the withdrawal, and reasons, to the participant's GP.

5.8.6 Informed consent

Informed consent is an ongoing issue, particularly with regard to a course of treatment or consultation with multiple appointments. The BAcC and BANT codes of practice require the practitioner to seek informed consent for all elements of treatment/advice offered on an ongoing basis. This will be refreshed in a Training Day for practitioners and incorporated into a study contract. To take account of this, the study excludes participants with conditions that are likely to compromise the ability to give informed consent on an ongoing basis.

5.8.7 Inconvenience and burden

The study unavoidably presents some inconvenience and burden to participants. This takes the following forms:

5.8.7.1 Travel to appointments (acupuncture group only)

This is clearly set out in the Participant Information Sheet. To mitigate this, participants will be offered a flat £5 offset against travel costs for each appointment attended.

5.8.7.2 Time given to appointments and assessments.

The total time commitment for each participant pathway is set out in the Participant Information Sheet. Efforts to mitigate this in assessments include a clear design and layout for questionnaires to minimise the time taken to complete, and the presence of the researcher online during the assessments so that any questions regarding completion of assessments can be asked and answered immediately.

5.8.7.3 Lifestyle change

Advice on lifestyle issues and support for behaviour change is an explicit part of the Santé-AF project. However, it is a requirement of the professional codes of practice set out by both the BAcC and BANT that respect for patient choice is central to the offering of lifestyle advice and the supporting of lifestyle change. Patients are not compelled in any way to act on lifestyle advice, but rather supported to carry out lifestyle change as a result of free choice. This is further emphasised in the Santé-AF study as a result of practitioner training during the training workshop before study commencement.

5.9 Potential harms to study personnel

- Practitioners carrying out treatments/consultations in a private setting are potentially at risk from participants who may be mentally or physically unstable, or who may make accusations against practitioners' professional probity. Such risk is within the normal scope of practice, and practitioners will be governed in their responses by codes of practice set out by their professional organisations. The Practitioners' Study Manuals set out the requirement for reporting any such incidents to the researcher and/or the Trial Steering Committee.
- The researcher may be at risk of Covid-19 transmission. To mitigate this, all study assessments will be held online. The equipment delivered to participants to enable them to carry out the study assessments will be isolated by the practitioner on

collection, thoroughly cleaned and isolated again before delivery to the following participant.

5.10 Benefits of participation

Whilst participants may not benefit directly from participating in the study, all participants are contributing to knowledge regarding possible treatments for AF.

All participants are contributing to the knowledge base regarding the condition of AF, as the dataset from the study will provide information regarding participant characteristics.

For those participants asked to wear a CardioSTAT® ambulatory ECG device during the study, there is potential benefit in undergoing additional monitoring of symptoms that are reported directly to the participant's GP.

5.11 Incidental medical findings (IMFs)

IMFs may be made at several key points in this study:

- During consultation with an acupuncturist or nutritional therapist;
- During online assessments with the researcher;
- During the operational period of the CardioSTAT® ambulatory ECG device (AED) for those participants randomised to wear one.

Note that for the purposes of this study, the definition of "incidental medical findings" is taken to include:

- "red flags" (Welch, 2011) (as detectable within the remit of a standard acupuncture treatment or online nutritional therapy consultation, or online study assessment), if not already known to the patient's GP or other healthcare practitioner. Note that these may not be connected with the patient's AF. In such cases, the patient will be asked whether the GP is already aware of the sign/symptom in question; if not, they will be contacted by letter (consent is explicitly sought in the Consent Form).
- any disclosure by the participant indicating that they may be a danger to themselves or others. In such cases, the patient's GP will be contacted by letter (over-riding consent is explicitly sought in the Consent Form);

- any features of the data gathered by the CardioSTAT® heart monitor and analysed by Icentia technicians. Data from the CardioSTAT® monitors is screened by a cardiac physiologist employed by the manufacturer, Icentia Limited, and IMFs (known by Icentia as "priority events") are reported to the study's consultant cardiologist (SG), who will make an appropriate referral according to his professional judgement. All data is made available to the participant's GP via the Icentia web interface.

All IMFs will be reported immediately to the researcher (KC), who will:

- report onwards to the Trial Steering Committee; and
- follow up with the GP regarding continuation of the participant in the study.

5.12 Outcome measures and methods

Table 6 shows the outcome measures applied at each measurement point, together with the instrument used, type of data gathered and an indication of the data analysis plan.

The primary outcome measures of the future trial (subject to feasibility data) are:

- To assess level of symptoms:

- The AF-FDS 7-day symptom diary, a non-validated data collection tool for AF symptoms by self-report;
- The CardioSTAT® 7-day heart monitor, a CE-marked device being used for its intended purpose to collect data on AF symptoms by ECG monitoring (Macfarlane, 2020).

- To assess quality of life:

- The EQ-5D-5L health and quality of life questionnaire, a validated data collection tool for assessing general quality of life;
- The Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) questionnaire, a validated data collection tool for assessing AF-related quality of life.

In this study, outcome measures are not applied to gather data *per se,* as would be the case in a future larger-scale trial, but rather to gain insights into the feasibility of applying these measures, in the described manner, at the specified points, for this population.

5.12.1 Study assessment table

Table 6 (Study Assessment Table) sets out the outcome measures applied to which subset of study population at a given time point, together with the instruments used and an indication of the analysis plan.

Table 6: Study Assessment table

LINE #	OBJECTIVE EVALUATED	PRE-STUDY / BASELINE	END OF INTERVENTION (EOI)
1	Objective 1: Participants' willingness to be randomised	**Data gathered:** Reasons for decision to participate. **Instrument**: Questionnaire (all participants). Interview for sub-set of participants. **Analysis (qual):** reflexive thematic analysis (Braun and Clarke, 2019; Gough, 2017) **Analysis (quant):** Descriptive statistics.	–
LINE #	**OBJECTIVE EVALUATED**	**PRE-STUDY / BASELINE**	**END OF INTERVENTION (EOI)**
2	Objective 1: Participants' willingness to be randomised	**Data gathered:** Reasons for decision not to participate. **Instrument:** Permission to Approach & Consent Forms **Analysis (qual):** reflexive thematic analysis.	–
LINE #	**OBJECTIVE EVALUATED**	**PRE-STUDY / BASELINE**	**END OF INTERVENTION (EOI)**
3	Objective 1: Participants' willingness to be randomised	**Data gathered:** Number of randomised participants versus totals eligible. **Instrument:** Primary care screening logs **Analysis (quant):** descriptive statistics; calculation of ratios at each stage.	–
LINE #	**OBJECTIVE EVALUATED**	**PRE-STUDY / BASELINE**	**END OF INTERVENTION (EOI)**
4	**Objective 2:** Appropriateness of eligibility criteria (practitioners)	**Data gathered:** Number of practitioners recruited versus total and eligible. Reasons for exclusion and non-recruitment **Instrument:** cross-sectional survey. **Analysis (quant):** descriptive statistics; calculation of ratios at each stage; content analysis of reasons for exclusion	–

LINE #	OBJECTIVE EVALUATED	PRE-STUDY / BASELINE	END OF INTERVENTION (EOI)
5	**Objective 2:** Appropriateness of eligibility criteria (participants)	**Data gathered:** Number of participants recruited versus total and eligible. Reasons for exclusion and non-recruitment **Instrument:** recruitment documents **Analysis (quant):** descriptive statistics; calculation of ratios; content analysis of reasons for exclusion	–
LINE #	**OBJECTIVE EVALUATED**	**PRE-STUDY / BASELINE**	**END OF INTERVENTION (EOI)**
6	**Objective 2:** Appropriateness of eligibility criteria	**Data gathered:** Participant characteristics for comparison with other AF cohorts. **Instrument**: Screening phone call questionnaire and baseline questionnaire. **Analysis (quant)**: symmetric correlation tests between Sante-AF cohort and comparable AF cohorts	–
LINE #	**OBJECTIVE EVALUATED**	**PRE-STUDY / BASELINE**	**END OF INTERVENTION (EOI)**
7	**Objective 3**: Participant retention	**Data gathered:** Number of recruited participants vs total approached. **Quant**: calculation of % retained at baseline	**Data gathered:** Number of retained participants vs total randomised. **Quant**: calculation of % retained at EOI; paired samples t-test for differences between time-points
LINE #	**OBJECTIVE EVALUATED**	**PRE-STUDY / BASELINE**	**END OF INTERVENTION (EOI)**
8	**Objective 3**: Participant retention	**Data gathered:** Dates of SMS compliance prompts + numbers of returned measures for each prompt. **Analysis (quant)**: calculation of % of returned measures for each prompt.	**Data gathered:** Dates of SMS compliance prompts + numbers of returned measures for each prompt. **Analysis (quant)**: calculation of % of returned measures for each prompt; paired samples t-test for differences between time-points
LINE #	**OBJECTIVE EVALUATED**	**PRE-STUDY / BASELINE**	**END OF INTERVENTION (EOI)**
9	**Objective 3**: Participant retention	–	**Data gathered:** Reasons for withdrawal. **Instrument**: Questionnaire for leavers **Analysis (qual)**: Reflexive thematic analysis.

LINE #	OBJECTIVE EVALUATED	PRE-STUDY / BASELINE	END OF INTERVENTION (EOI)
10	**Objective 3**: Participant retention	–	**Data gathered:** Reasons for retention. **Instrument**: Questionnaire for all participants; Interview for sub-set of participants **Analysis (qual)**: Reflexive thematic analysis.
LINE #	**OBJECTIVE EVALUATED**	**PRE-STUDY / BASELINE**	**END OF INTERVENTION (EOI)**
11	Objective 4: Acceptability of interventions	**Data gathered:** Participant report of allocation satisfaction/intervention expectation. **Instrument**: SMS poll **Analysis (quant)**: (1) descriptive statistics to indicate levels of satisfaction/expectation per group; (2) Spearman's correlation to determine direction and strength of relationship between allocation satisfaction and intervention expectation; (3) one-way between-subjects ANOVA for differences in satisfaction between groups; (4) Kruskal-Wallis H Test for differences in intervention expectation between groups.	_
LINE #	**OBJECTIVE EVALUATED**	**PRE-STUDY / BASELINE**	**END OF INTERVENTION (EOI)**
12	Objective 4: Acceptability of interventions	–	**Data gathered:** Participant report of acceptability of intervention. **Instrument**: questionnaire for all participants; Interview for sub-set of participants **Analysis (qual)**: Reflexive thematic analysis. **Analysis (quant)**: (1) descriptive statistics to indicate levels of acceptability per group; (2) one-way between-subjects ANOVA for differences in acceptability between groups.

LINE #	OBJECTIVE EVALUATED	PRE-STUDY / BASELINE	END OF INTERVENTION (EOI)
13	Objective 4: Acceptability of interventions	–	**Data gathered:** Participants' experience of self-care activity **Instrument:** questionnaire for all participants; interview for sub-set of participants **Analysis (qual)**: Reflexive thematic analysis. **Analysis (quant):** (1) descriptive statistics to indicate experience of self-care per group; (2) one-way between-subjects ANOVA for differences in experience of self-care between groups.
LINE #	**OBJECTIVE EVALUATED**	**PRE-STUDY / BASELINE**	**END OF INTERVENTION (EOI)**
14	Objective 4: Acceptability of interventions	–	**Data gathered:** Practitioner report of participant attendance. **Instrument**: Log books **Analysis (quant)**: (1) descriptive statistics to indicate levels of attendance per group; (2) one-way between-subjects ANOVA for differences in attendance between groups.
LINE #	**OBJECTIVE EVALUATED**	**PRE-STUDY / BASELINE**	**END OF INTERVENTION (EOI)**
15	**Objective 5**: Acceptability of participant assessments	**Data gathered:** Quantitative assessment of completeness of returned participant data. **Instrument**: via returned questionnaire. **Analysis (quant)**: Calculation of percentage completeness across groups; descriptive statistics to indicate levels of completeness per group; one-way between-subjects ANOVA for differences in completeness between groups	**Data gathered:** Quantitative assessment of completeness of returned participant data. **Instrument**: via returned questionnaire. **Analysis (quant)**: Calculation of percentage completeness across groups; descriptive statistics to indicate levels of completeness per group; one-way between-subjects ANOVA for differences in completeness between groups; paired samples t-test for differences in completeness between time-points

LINE #	OBJECTIVE EVALUATED	PRE-STUDY / BASELINE	END OF INTERVENTION (EOI)
16	**Objective 5**: Acceptability of participant assessments Note: Data in this section is gathered not to analyse for effectiveness but to evaluate feasibility of data gathering itself. Data marked * relates to effectiveness and therefore will be gathered in this feasibility study but will not be analysed for the feasibility study. Analysis details have therefore not been given here, except where they relate to data analysed for the feasibility study.	Data gathered: 1. Participant report of acceptability of assessments; *2. Participants' AF-related symptoms; *3. Participants' AF frequency, duration and severity in 7-day period; *4. Participants' level of satisfaction with allocated intervention group; *5. Participants' expectation of intervention effect; *6. Participants' anthropometric data (waistline/hip measurement, height, weight); BP; current medications. *7. Participants' general health data *8. Participants' AF-related quality of life (AFEQT) *9. General quality of life (EQ-5D-5L) *10. Health resource usage; current care-seeking behaviours; self-care behaviours. *11. Participants' experience of AF, and of current treatments Instrument: 1. Questionnaire for all participants & semi-structured interview for 26% of participants; 2, 7, 8, 9, 10. Questionnaire for all participants; 3. CardioSTAT® ambulatory ECG device (33% of participants) and AF-FDS diary (all participants); 4, 5. SMS poll; 6. Online assessment; 11. Semi-structured interview (26% of participants) Analysis: 1. Reflexive thematic analysis (qual data); descriptive statistics for levels of acceptability per group; one-way between-subjects ANOVA for differences in levels of acceptability between groups.	Data gathered: 1. Participant report of acceptability of assessments; *2. Participants' AF-related symptoms; *3. Participants' AF frequency, duration and severity in 7-day period; *4. Participant report of acceptability of intervention and self-care advice; *5. Participants' anthropometric data (waistline/hip measurement, height, weight); BP; current medications; *6. Participants' AF-related quality of life (AFEQT) *7. General quality of life (EQ-5D-5L) *8. Health resource usage; current care-seeking behaviours; self-care behaviours. Instrument: 1, 4. Questionnaire for all participants & semi-structured interview for 26% of participants; 2, 6, 7, 8. Questionnaire for all participants; 3. CardioSTAT® ambulatory ECG device (33% of participants) and AF-FDS diary (all participants); 5. Online assessment; Analysis: 1. Reflexive thematic analysis (qual data); descriptive statistics for levels of acceptability per group; one-way between-subjects ANOVA for differences in levels of acceptability between groups; paired samples t-test for differences in levels of acceptability per group between time-points.

LINE #	OBJECTIVE EVALUATED	PRE-STUDY / BASELINE	END OF INTERVENTION (EOI)
17	**Objective 6**: Utility of ambulatory ECG devices (AEDs)	**Data gathered:** Participants' AF symptom data **Instrument**: CardioSTAT® AED and AF-FDS 7-day self-report symptom diary **Analysis**: Qualitative/count data evaluation of correlation between AED and symptom diary.	**Data gathered:** Participants' AF symptom data **Instrument**: CardioSTAT® AED and AF-FDS 7-day self-report symptom diary **Analysis**: Qualitative/count data evaluation of correlation between AED and symptom diary.
LINE #	**OBJECTIVE EVALUATED**	**PRE-STUDY / BASELINE**	**END OF INTERVENTION (EOI)**
18	**Objective 6**: Utility of ambulatory ECG devices (AEDs)	**Data gathered:** Participant report on influence of CardioSTAT® on decision to participate. **Instrument**: questionnaire **Analysis (quant)**: Descriptive statistics for all participants.	**Data gathered:** Participant report on influence of CardioSTAT® on decision to remain in study. **Instrument**: questionnaire **Analysis (quant)**: Descriptive statistics for all participants.
LINE #	**OBJECTIVE EVALUATED**	**PRE-STUDY / BASELINE**	**END OF INTERVENTION (EOI)**
19	**Objective 7**: Experience of study participation (for practitioners)	–	Practitioners' experience of study participation. **Instrument**: Online focus group **Analysis (qual)**: reflexive thematic analysis.
LINE #	**OBJECTIVE EVALUATED**	**PRE-STUDY / BASELINE**	**END OF INTERVENTION (EOI)**
20	**Objective 7**: Experience of study participation (for participants)	**Data gathered:** Participants' experience of study participation. **Instrument**: Semi-structured interview (sub-set of participants) **Analysis (qual)**: Reflexive thematic analysis.	**Data gathered:** Participants' experience of study participation. **Instrument**: Semi-structured interview (sub-set of participants) **Analysis (qual)**: Reflexive thematic analysis.
LINE #	**OBJECTIVE EVALUATED**	**PRE-STUDY / BASELINE**	**END OF INTERVENTION (EOI)**
21	**Objective 7**: Experience of study participation	**Data gathered:** Participants' experience of study participation. **Instrument**: questionnaire **Analysis (qual)**: reflexive thematic analysis. **Analysis (quant)**: Descriptive statistics for all participants.	**Data gathered:** Participants' experience of study participation. **Instrument**: questionnaire **Analysis (qual)**: reflexive thematic analysis. **Analysis (quant)**: Descriptive statistics for all participants.

LINE #	OBJECTIVE EVALUATED	PRE-STUDY / BASELINE	END OF INTERVENTION (EOI)
22	**Objective 8**: Viability of all objectives at a time of global pandemic	**Data gathered:** Participants' status re. COVID/vaccination, and feelings about study participation during the pandemic. **Instrument**: questionnaire for all participants; semi-structured interview for sub-set of participants **Analysis (qual)**: reflexive thematic analysis. **Analysis (quant)**: Descriptive statistics for all participants.	**Data gathered:** Participants' status re. COVID/vaccination, and feelings about study participation during the pandemic. **Instrument**: questionnaire for all participants; semi-structured interview for sub-set of participants **Analysis (qual)**: reflexive thematic analysis. **Analysis (quant)**: Descriptive statistics for all participants.

5.13 Data collection: methods and locations

Methods of data gathering are fully set out in Table 6, relative to the Objective they are assessing. Table 7 below shows methods, location and timings.

Table 7: Data collection methods, location and timings

Data compiler(s)	Data collection method	Data collection location	Data collection timing
Researcher / practitioners	Telephone/internet survey	University of York / Researcher's home	Pre-randomisation period
Primary care staff	Screening logs	Primary care premises	Pre-randomisation period
Participants	Screening questionnaire (by telephone)	Participants' usual living environments plus University of York / Researcher's home	Pre-randomisation period
Participants / non-participants	Various participant-facing documents, including consent forms and permission to approach documents	Participants' usual living environments	Pre-randomisation period
Participants / researcher	SMS poll	Participants' usual living environments	Post-randomisation period
Participants	Self-report questionnaires	Participants' usual living environments (online) University of York / Researcher's home	Baseline End-of-intervention
Participants	Self-report diaries	Participants' usual living / working environments	Baseline End-of-intervention
Participants / Icentia Limited	Ambulatory ECG devices	Participants' usual living / working environments	Baseline End-of-intervention
Participants Researcher	Measurements and medication log	Participants' usual living environments (online) University of York / Researcher's home	Baseline End-of-intervention
Participants (sub-set) / Researcher	Qualitative interviews	Participants' usual living environments (online) University of York / Researcher's home	Baseline End-of-intervention
Practitioners	Intervention log books	Practitioners' premises	At each intervention
Practitioners / Researcher	Focus groups	Location of practitioner's choice (online)	End-of-intervention

		University of York / Researcher's home	

5.14 Data analysis plan

Both quantitative and qualitative methods are used to analyse data gathered by the study in a concurrent mixed methods approach (Creswell and Creswell, 2018; Morse, 1991) to enable a full understanding of both *whether* specific elements of the trial's design are, or are not, feasible, and *why* this is so. The combination of both types of data allows a thorough assessment of feasibility, and the application of the ADePT decision-making process (Bugge et al., 2013) to identify and recommend changes to a future trial.

5.14.1 Quantitative methods

The intent of quantitative analysis is to yield an understanding of whether a given aspect of the future trial design is feasible.

Quantitative methods used are set out in Table 6, in relation to the Objectives they answer. They include correlation tests, descriptive statistics and one-way/two-way between-subjects ANOVA tests. This range of tests will provide an understanding of the various aspects of feasibility (as listed in the Objectives), including any changes over time.

Table 8, below, shows cut-off points for feasibility.

5.14.2 Qualitative methods

Qualitative methods used are set out in Table 6, in relation to the Objectives they answer. The intent of qualitative analysis is to gather an understanding of *why* a given aspect of the future trial design is, or is not, feasible.

In keeping with the pragmatic nature of the research question, an inductive analysis approach will be taken; themes are allowed to emerge from the data, and relationships between themes can be elucidated (Blaikie, 2007). Qualitative data indexing software (NVivo) (QSR International, 2019) will facilitate analysis.

Data will be analysed using a reflexive thematic analysis approach (Braun and Clarke, 2019), in which the researcher "strives to be fully cognisant of the philosophical sensibility and theoretical assumptions informing their use of TA… [reflexive TA is] about the researcher's reflective and

thoughtful engagement with their data and their reflexive and thoughtful engagement with the analytic process" (ibid., 594). As such, the choice of reflexive TA as an analytic approach aligns with the social constructivist, pragmatic approach of the study.

Qualitative data analysis will also include a limited use of comparative content analysis (Hseih and Shannon, 2005) to detect changes in qualitative data over time.

5.14.2.1 A note on interviews

In-depth semi-structured interviews will be held to gather some qualitative data from participants; these are appropriate to the phenomenon investigated, i.e., the nature of the participant's experience of study participation and their intervention. Interviews will be audio-recorded, and field notes will be written up immediately after each interview.

Interview topic guides (ITGs) were developed with a panel of two AF patients and one lay member of the public (National Institute for Health Research, 2014). Questions are open-ended, broad and general to allow participants to convey and construct personal meanings (Creswell and Poth, 2018). The baseline and end-of-intervention ITGs were piloted with the two AF patients, following which they were modified in view of feedback. The ITGs will be applied flexibly in each interview – while all areas will be explored, the nature of the individual participant's reality will be allowed to direct those areas to which more focus is given.

5.15 Synthesis

5.15.1 Integrating mixed methods data

Integrating the quantitative analysis and qualitative interpretations will be carried out using a methodological triangulation approach (Farmer et al., 2006) to establish convergent validity.

5.15.2 Criteria for feasibility and progression to a future trial

The CONSORT guidelines for reporting pilot or feasibility studies (2016) suggest that evaluation of stand-alone pilot or feasibility studies should focus on the descriptive analysis of key feasibility objectives such as recruitment levels, intervention adherence and attrition. Table 6 above shows the ways in which the objectives for this study are evaluated.

Cut-off points for feasibility objectives (i.e., the thresholds at which an aspect of trial design was considered feasible for a larger trial) were set using a range of relevant precedents. Table 8 (next page) shows the objective, the item measured, the cut-off point and rationale.

The ADePT process (Bugge et al., 2013) will be applied to determine which design features should be changed, and to recommend changes. Finally, Avery and colleagues' traffic light system (2017) will be used to indicate the overall recommendation for progression to a future trial.

5.16 Changes to feasibility study assessments/measurements after study start

As a feasibility study, exploratory adjustments may be made in order to test aspects of the trial design relating to the Objectives. Any exploratory adjustments will be described, together with rationale for adjustments, and evaluated alongside the overall evaluation of the primary Aim.

5.17 Sample size calculations for numbers of participants

Many sources suggest that a formal sample size calculation is not required for a feasibility study (Eldridge et al., 2016). Nonetheless, in this study a sample size has been calculated on the basis of a one-sided 80% confidence interval and the proposed sample size of the future larger-scale trial (Cocks and Torgerson, 2013). A one-sided CI is used on the basis that a future larger-scale trial will not take place if there is evidence of harms associated with the interventions, and therefore a two-sided CI is redundant. An 80% power level gives a reasonable compromise between the power of the feasibility study on the one hand, and on the other, the time, costs and potential ethical issues.

5.17.1 Sample size calculation for a future larger-scale trial

For the AFEQT AF-related quality of life scale, Spertus et al. (2011) determined that the median value for change in mean scores for the Overall score (an aggregate of the first three domains of the scale) at 3 months is 9.8 points (9.8%), and the corresponding standard deviation of mean scores is 21. This gives a standardised effect size of 0.466.

To detect this effect size at a power of 80% with a significance level of 5% requires an approximate sample size of 147 participants. Adjusting this across three groups gives a total sample size of approximately 220 participants. Adjusting again for an estimated 20% loss to follow-up yields 264 participants in total, or 88 in each of the three groups. Finally, adjusting for a 2:2:1 allocation ratio in favour of the intervention groups gives a per-group total of 106:106:53.

Table 8: Cut-off points for feasibility

	Objective	Measurement	Cut-off point	Rationale
1	Participants' willingness to be randomised	Percentage of eligible participants randomised (continuous data)	⩾ 90%	Survey of recent similar trials (see Appendix 1)
2	Appropriateness of eligibility criteria	Demographic and clinical characteristics of randomised participants (descriptive statistics)	⩽ 20% difference	Comparison with recent AF characteristics studies (Camm et al., 2016; de Groot et al., 2020; Savickas et al., 2020)
		Percentage of identified participants eligible (continuous data)	⩾ 60%	Survey of recent similar trials (see Appendix 1)
3	Participant retention	Percentage of randomised participants retained (continuous data)	⩾ 80%	Survey of recent similar trials (see Appendix 1)
4	Acceptability of interventions	Participant report of allocation satisfaction (descriptive statistics per group)	⩾ 75% reporting 7-10 on 10-point scale (10 = most satisfied)	Jobst, Leppla and Köberich, 2020
	Acceptability of interventions	Participant report of acceptability of intervention (descriptive statistics)	⩾ 75% reporting 1-3 on 7-point scale (1 = most acceptable)	Jobst, Leppla and Köberich, 2020
5	Acceptability of participant assessments	Completeness of questionnaires and assessment data collected (descriptive statistics)	⩾ 80% of all data collected	Jobst, Leppla and Köberich, 2020
		Participant report of acceptability of assessment (descriptive statistics)	⩾ 90% reporting 1-3 on 7-point scale (1 = most acceptable)	Jobst, Leppla and Köberich, 2020
6	Utility of ambulatory ECG devices (AEDs)	Number of AF episodes recorded by AEDs not noted on AF symptom diary (continuous data)	⩾ 1	–
		Participant report of influence of AEDs on decision to participate in study (descriptive statistics)	⩾ 50% reporting 1-2 on 5-point scale (1 = most influential)	–
7	Participant experience of study participation	Participant report of acceptability of study participation (descriptive statistics)	⩾ 75% reporting 1-3 on 7-point scale (1 = most acceptable)	–
8	Feasibility of all objectives at a time of global pandemic	Cumulative total of all the above objectives (except #6)	See above	–
		Participant report of worry regarding COVID-19 cross-infection as a result of being in the study	⩾ 75% reporting no worry	–
		Patient report of COVID-19 as a reason to decline participation	⩾ 20% reporting COVID-19 as a factor in decision not to participate	–

5.17.2 Sample size calculation for the feasibility study

Applying Cocks and Torgerson's CI-based formula: taking the standardised effect size of a future larger-scale trial as 0.466, calculated at 80% power and a 5% significance level, the feasibility study sample size can be set at a total of approximately 24 participants across the three groups. Adjusting for 20% attrition yields 29 participants (rounded to 30 for convenience). Adjusting again for the 2:2:1 allocation ratio in favour of the intervention groups gives a per-group total for the feasibility study of 12:12:6.

5.18 Sampling strategy for qualitative investigations

5.18.1 Sampling strategy for participant interviews

The first qualitative sample frame is small ($\leqslant$30) and non-probabilistic (comprising a first sample of those participants who are willing to be interviewed); those selected for interview will be a sub-set of those who are judged from a short interview conducted during the screening phonecall to be able to communicate reasonably coherently, expressively and reflectively. For this reason, a purposive sampling strategy of maximal variation (Palinkas et al., 2015) will be used to mitigate the effect of selection bias. Participants will be selected from within each study arm according to the maximum variation possible across four key characteristics: age, gender, length of diagnosis, and previous experience of complementary therapies (using data gathered from the interview conducted during the screening phonecall).

5.18.1.1 A note on sample size for participant interviews (feasibility study)

Three participants will be selected from each of the intervention arms, and two from the usual care group, giving a total of eight participants (just under 27% of the total participants). This represents the maximum achievable total within the resources available to the study. However, each participant varies characteristically from all others; additionally, the sampling strategy of maximal variation calls for 16 participants, while the maximum achievable total in this study is just eight.

For these reasons, it is possible that code and/or meaning saturation may not be reached (Hennink, Kaiser and Marconi, 2017). If new codes and/or meanings are still emerging as end-of-data is reached, the implications of this for the findings will be critically discussed.

5.18.2 Sampling strategy for focus groups (feasibility study)

Focus groups will be conducted for practitioners delivering the interventions (including separate groups for acupuncturists and for nutritional therapists). The entirety of each cohort will be invited to the appropriate focus group in an attempt to minimise selection bias.

5.19 Blinding

This feasibility study is conducted in preparation for an 'open' trial: given the nature of the interventions, neither practitioners nor participants can be blinded to the intervention they are giving or receiving.

Additionally, it is not possible to blind *most* outcomes assessors:

- **Participants** will self-report some outcomes using the baseline, end of intervention and final follow-up questionnaires. They will naturally be aware of the intervention received;
- The **researcher** will inevitably be aware of the intervention received (see Concealing the random allocation sequence). She will gather and analyse a wide variety of post-randomisation data including:
  - Patients' anthropometric data, blood pressure and medications data via online assessment sessions;
  - AF frequency, duration and severity via AED monitors and AF symptom diary;
  - SMS compliance prompt data;
  - Participant report of allocation satisfaction and expectation of intervention;
  - Participant reasons for participation, retention and withdrawal;
  - Data from baseline, end of intervention and final follow-up questionnaires, including completeness;
  - Data from qualitative interviews (in which knowledge of intervention received will be necessary to conduct interviews);
  - Participant attendance at intervention appointments and online assessments;
  - Completeness of returned participant questionnaires;
  - Participants' experience of study participation (including practitioners).

The single outcome assessor that will be blinded is Icentia Limited, which will process data from the CardioSTAT® AEDs without knowledge of the intervention received.

5.20 Pseudonymisation of participants

In addition to the procedures outlined in Table 6, the following confidentiality provision applies:

Participants are pseudonymised by unique study ID number (a randomly generated 3-character numeric code) at the point of conducting the screening phone call (i.e., after the Consent Form has been signed and returned). The study ID number is used as the sole means of identification of the participant to all individuals associated with the study except:

1. where it is necessary to communicate with the participant either for study progress reasons, as set out in Table 6 below;
2. where there is evidence of serious adverse events or incidental medical findings;
3. study practitioners will naturally know the identity of participants treated by them. Strict confidentiality is a requirement of both the BAcC and BANT. Sharing of information between the study's practitioners and the researcher is explicitly consented in the Consent Form.

5.21 Trial management

5.21.1 Study management

The study will be managed by the researcher, Karen Charlesworth, under the supervision of her academic supervisors Dr Judith Watson and Professor David Torgerson, who are located within York Trials Unit, a UKCRC registered clinical trials unit.

5.21.2 Trial Steering Committee

The Trial Steering Committee (TSC) comprises the membership set out in Study personnel, above.

5.21.2.1 Trial Steering Committee: Terms of Reference

These Terms of Reference (ToRs) apply to the Trial Steering Committee (TSC) of the Santé-AF Feasibility Study (ISRCTN 13671984).

The TSC provides advice to the researcher, the study's sponsor representative and the study's funders on all appropriate aspects of the study.

As the study is a doctoral research project, much oversight is given by the researcher's academic supervisors (Dr Judith Watson and Professor David Torgerson, University of York Health Sciences department). This oversight over-rides that of a regular TSC, and relieves the Santé-AF TSC of some responsibilities, specifically the following:

- approving the protocol and study documentation, including any amendments;
- monitoring recruitment rates;
- monitoring study data collection;
- monitoring follow-up rates;
- timely reporting of study results;
- approval of the statistical analysis plan;
- approval of the publication policy and any publications;
- approval of external or early internal requests for release of data.

The Santé-AF TSC's particular focus is:

- patient safety, particularly with respect to COVID-19;
- consideration of new information relevant to the research question.

The Santé-AF TSC's abiding and over-riding focus is the safety and wellbeing of study participants. This should take precedence over the interests of science and any interests of society served by the study.

Membership of the Santé-AF TSC comprises:

- a Chair with research and trials expertise;
- an expert acupuncturist member;
- an expert nutritional therapist member;
- an expert cardiologist member;
- the researcher (*ex officio*);

- a representative of the sponsor (from the University of York Contracts & Sponsorship department).

See Study personnel for more information on TSC members.

The Santé-AF TSC meets on an as-needed basis to discuss:

- issues of participant safety. These may be prompted in a number of ways, including incidental medical findings reported by practitioners, the researcher, study participants or the study's supplier of ambulatory ECG devices (AEDs) and AED data processing services Icentia Limited;
- issues related to the local incidence of Covid-19, including the monitoring of the local R-rate and registered number of cases over the most recent 7 days, on a weekly basis. If the R-rate for the North-East and Yorkshire (as set out in https://www.gov.uk/guidance/the-r-number-in-the-uk) in the previous 7 days reaches an average of 1.1 between the lower and upper bounds; and the average daily number of new local cases in the previous 7 days in the York area (as set out in https://coronavirus.data.gov.uk/details/cases?areaType=utla&areaName=York) exceeds 70, the trial's acupuncture arm will be paused for a duration at the discretion of the TSC. Alternatively, the acupuncture arm will be paused if the UK government declares a Tier 4 lockdown (or above) applicable to the York area. Note that the Nutritional Therapy arm of the trial will proceed as planned, as all practitioners are working online with no face-to-face contact;
- issues of emergent information that may impact on the relevance of the research question. These issues may be prompted in a number of ways, including the awareness of any study personnel.

Responsibility for convening TSC meetings lies with the researcher. Exceptionally, the Chair of the TSC or the study sponsor or funder(s) may convene TSC meetings.

Representatives of the study's funders are invited to all TSC meetings.

The TSC will maintain confidentiality of all study information that is not already available in the public domain.

5.21.3 Data management

This study abides by the principle of data protection by design and default. To reduce risk and demonstrate compliance with GDPR (European Parliament and Council of the European Union, 2018), it uses appropriate pseudonymisation, data minimisation, limitation and protection of storage, access restrictions, and organisational measures, as set out in Table 9.

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

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

Table 9: Data management

	What data is gathered, why, and in what format?	Where will it be stored and transferred, and what arrangements are made for anonymising/ confidentiality?	How long will it be stored for, and who will access it?
(a) Initial screening data from registry	**Data gathered:** Patient characteristics data via IT search in primary care records to identify potential participants based on eligibility criteria (see Table 1 & 2). **Rationale:** Data is screened by GPs (i.e., direct care team) to avoid any ethical issue with other individuals having access to medical records. Anonymised numerical records will be kept, setting out: total patients with AF; total eligible for study at initial screening stage; total sent information pack; reasons for non-eligibility. **Format**: electronic format (Excel spreadsheet)	Anonymised log will be stored securely by GP surgery and transferred to the researcher via email after the recruitment period has ended.	Data will be stored for 10 years from the date of study commencement. Electronic documents will be securely destroyed following UoY protocol (University of York Records Management & Information Governance Office, 2010) **Access**: The researcher and academic supervisors/assessors will access this data.

(b): Personal identification data	**Data gathered**: Participants' name, address, telephone numbers, email address. Participants' nominated mobile phone number and date of birth. **Rationale**: To identify/include relevant participants and facilitate communication during the study. **Format:** Hard copy format; electronic format following data entry.	Hard copies will be stored in the Department of Health Sciences according to principles set out in Storing Active Research Data (University of York Records Management & Information Governance Office, 2018). By its nature, this data must remain personally identifiable. Data will be entered into an Excel spreadsheet by the researcher on an encrypted laptop; this file will be password-protected and stored in the University-provided personal Filestore. Some personal identification data (name, mobile phone number) will be stored in an online SMS management tool (NHS DSP Toolkit compliant) via an encrypted laptop.	Electronic data will be stored until assessment of the PhD project is complete. Hard copy will be stored for 10 years after date of collection. Both types of document will be securely destroyed following UoY protocol (University of York Records Management & Information Governance Office, 2010) Information stored in the FireText online account will be deleted when assessment of the PhD project is complete. **Access**: Only the researcher will access this data.
(c) Personal information about health: self-reported screening data	**Data gathered:** Patients' self-reported information on eligibility criteria recorded by the researcher during a phonecall with the participant. **Rationale**: To identify/include relevant participants. **Format**: Hard copy format for data gathering; electronic format following data entry.	Separate pseudonymised screening questionnaire completed for each patient. Hard copies will be stored in the Department of Health Sciences according to principles set out in Storing Active Research Data (University of York Records Management & Information Governance Office, 2018). Pseudonymised records will be noted in Excel spreadsheet on an encrypted laptop by the researcher; this will be password-protected and stored in the University-provided personal Filestore.	Data will be stored for 10 years from date of study commencement. Documents will be securely destroyed following UoY protocol (University of York Records Management & Information Governance Office, 2010). **Access**: The researcher and academic supervisors/ assessors will access this data.
(d) Personal information about health: data from consultations	**Data gathered**: Practitioners' information on treatments/ advice given to participants. **Rationale**: To check feasibility of gathering this data, and quality of data gathered. **Format:** Hard copy format for data gathering; electronic format following data entry.	Practitioners will keep treatment log for each patient, then return to researcher at end of intervention by registered post. Hard copies will be stored in the Department of Health Sciences according to principles set out in Storing Active Research Data (University of York Records Management & Information Governance Office, 2018). Pseudonymised records will be noted in an Excel spreadsheet on an encrypted laptop by the researcher; this will be password-protected and stored in the University-provided personal Filestore.	Data will be stored for 10 years from date of study commencement. Documents will be securely destroyed following UoY protocol (University of York Records Management & Information Governance Office, 2010). **Access**: The researcher and academic supervisors/ assessors will access this data.

(e) Personal information about health: data from participant assessments	**Data gathered**: Participants' information on aspects of physical, emotional and mental health recorded on questionnaires, qualitative interviews and record sheets at two study measurement points. **Rationale**: To check feasibility of gathering this data, and quality of data gathered. **Format**: Questionnaires in hard copy format; Interviews audio-recorded; Record sheets in electronic format. All transcribed into electronic format following data entry.	Pseudonymised hard-copy questionnaires will be stored in the Department of Health Sciences according to principles set out in Storing Active Research Data (University of York Records Management & Information Governance Office, 2018). Audio recordings will be erased immediately after transcription (see below). Pseudonymised data will be transcribed into Word documents by the researcher on an encrypted laptop; these will be password-protected and stored in the University-provided personal Filestore.	Data will be stored for 10 years from date of study commencement. Documents will be securely destroyed following UoY protocol (University of York Records Management & Information Governance Office, 2010). **Access**: The researcher and academic supervisors/ assessors will access this data.
(f) Personal information about health: Icentia CardioSTAT® ECG device data	**Data gathered:** by Icentia CardioSTAT® ECG devices worn by 33% of participants at three study measurement points. **Rationale**: To check feasibility of gathering this data, and quality of data gathered. **Format**: Electronic format.	Non-pseudonymised data will be made available to participants' GPs (explicitly consented by consent form) and the researcher using Icentia's secure interface. Note that 'priority events' (incidental medical findings in need of attention) will be reported direct by Icentia to the study's consultant cardiologist using participants' personally identifiable data (explicitly consented). Pseudonymised records will be noted in an Excel spreadsheet on an encrypted laptop by the researcher; this will be password-protected and stored in the University-provided personal Filestore.	Data will be stored for 10 years from date of study commencement. Documents will be securely destroyed following UoY protocol (University of York Records Management & Information Governance Office, 2010). **Access**: The researcher, the study consultant cardiologist*, personnel from Icentia Limited, participants' GPs* and academic supervisors/ assessors will access this data. *if needed due to incidental medical findings

(g) Miscellaneous data gathered during the study	**Data gathered:** Qualitative information regarding patients' reasons for not wanting to take part in study via Permission to Approach, Consent Form, LTFU letter and Leaver's questionnaire. SMS quantitative data gathered from all participants at post-randomisation phase on satisfaction and expectation. **Rationale:** Qualitative information: to inform future trial. SMS data: to check feasibility of gathering this data, and quality of data gathered. **Format:** Qualitative information in hard copy format. Electronic format following data entry. SMS data in electronic format via FireText interface.	Qualitative information: pseudonymised hard copies will be stored in the Department of Health Sciences according to principles set out in Storing Active Research Data (University of York Records Management & Information Governance Office, 2018). SMS messages will not be anonymised until transcription (see below). Messages are sent/received via FireText, an NHS Digital DSP Toolkit-compliant supplier of SMS communication services. Pseudonymised hard copy records and SMS data will be transcribed into an Excel spreadsheet by the researcher on an encrypted laptop; this will be password-protected and stored in the University-provided personal Filestore.	Data will be stored for 10 years from the date of study commencement. Both hard copy and electronic documents will be securely destroyed following UoY protocol (University of York Records Management & Information Governance Office, 2010). Some data will be held confidentially on the FireText interface and destroyed once academic assessment is complete. **Access**: The researcher and academic supervisors/assessors will access this data.
(h) Information gathered from practitioners regarding experience of study participation	**Data gathered:** Qualitative information from focus groups gathered via audio recording and note taking. **Rationale:** To inform future trial. **Format:** Audio recording; transcribed into electronic format.	Audio will be transcribed by the researcher on an encrypted laptop; these will be password-protected and stored using the University-provided personal Filestore. Practitioners will be pseudonymised in the transcriptions. Recordings will be held in the University-provided personal Filestore. They will be erased immediately after the academic assessment is complete.	Transcribed data will be stored for 10 years from the date of study commencement. Both hard copy and electronic documents will be securely destroyed following UoY protocol (University of York Records Management & Information Governance Office, 2010). **Access**: The researcher and academic supervisors/assessors will access this data.
(i) Study management information	**Data gathered:** Information regarding participant contact and response, and flow of study. **Rationale:** To aid the conduct of the study. **Format:** Electronic format.	Pseudonymised study management information will be identified only by participants' study ID numbers and stored in an Excel spreadsheet created on an encrypted laptop and stored in the University-provided personal Filestore. Pseudonymised details of Adverse Events and Incidental Medical Findings will also be recorded in electronic format on an encrypted laptop and stored in the University-provided personal Filestore.	Transcribed data will be stored for 10 years from the date of study commencement. Both hard copy and electronic documents will be securely destroyed following UoY protocol (University of York Records Management & Information Governance Office, 2010). Access: The researcher and academic supervisors/assessors will access this data.

5.22 Limitations and biases of this study

5.22.1 Limitations

Limitations associated with this study include:

- Feasibility testing of eligibility criteria (Objective 2) could be fully implemented due to the decision to test Objective 6, the value added by ambulatory ECG devices (AEDs): in order to measure value in terms of congruence between self-reported AF episodes and those detected by the AED, only patients with perceptible AF could be enrolled. This means that an important section of the AF patient population – patients with 'silent' or asymptomatic/non-perceptible AF – could not be included in the study population. As patients with silent AF make up a significant proportion of the AF population, this introduces an artificial exclusion criterion, a limitation in the testing of eligibility criteria, and the possibility of selection bias. This limitation has been mitigated by the requirement for each participating GP surgery to report on figures for total numbers of AF diagnoses which will be contrasted with numbers excluded due to non-perceptible AF. This will produce a guide to the numbers of patients eligible for a future trial if patients with diagnosed silent AF are to be included.
- The study sample is limited to participants between the ages of 45 and 70 with diagnosed AF, living in the north of England. As a result, the feasibility findings of this study may not be indicative of the feasibility of a future trial that includes other populations.
- Limitations on study funding meant that several aspects of trial feasibility could not be explored. Notably, this includes the availability of translators, which may exclude participants who do not speak English fluently; and the cap of £5 on travel expenses for participants in the acupuncture group attending appointments. As a result, the findings for recruitment objectives in this study may not be indicative of the feasibility of a future trial that has higher levels of funding.
- The final follow-up was planned for a six-month period; however, the limitations of the PhD timescale, coupled with the delays due to Covid-19, did not allow for a long final follow-up. Data is therefore collected at two time-points only (baseline and end of intervention). The fact that the final follow-up is now positioned at the end of the

intervention may produce an evaluation of participant retention that may not be generalisable to a future trial with a longer final follow-up period.

- COVID-19 may limit numbers of participants to those who are vaccinated or otherwise less vulnerable (or feeling themselves to be less vulnerable) to cross-infection. This may limit the generalisability of the study's findings in terms of the feasibility of a future trial that may not take place under pandemic conditions. However, at the time of writing, measures to reduce vulnerability are currently under way, including a programme of vaccination. This may reduce the numbers of participants who decline to participate due to anxiety regarding COVID-19 cross-infection.

5.22.2 Biases

Being a PhD study, almost all of the administration and trial management processes are carried out by the sole researcher (KC). The fact that there is only one researcher unavoidably adds potential biases.

However, the outcomes of this study are assessed and reported in terms of a future trial's feasibility, rather than effectiveness of the interventions. While bias may affect the evaluation of feasibility, it will not affect the evaluation of primary outcomes, as these will not in fact be evaluated; data for all outcomes are collected but only to test the feasibility of collection. In addition, a future trial would be the work of a multidisciplinary team and therefore mitigation against many types of potential bias will be incorporated into the trial design – notably including allocation bias, observer bias, and some forms of obsequiousness bias.

Table 10 shows possible biases affecting feasibility outcomes for this study may include the following. All will be critically discussed in the thesis.

Table 10: Possible biases and mitigations

Type of bias	Description of bias in Santé-AF study	Mitigation
Allocation bias and/or performance bias	The sole researcher/assessor cannot be blinded to allocation and may therefore be suspected of subverting this and/or assessing participants differently according to their group allocation.	To mitigate the former, integrity of randomisation can be verified, as all randomisations are logged by the sealedenvelope.com website. To mitigate the latter, all assessments may be verified by various means including recordings of all interviews; original completed questionnaires; and data from ambulatory ECG devices.
Attrition bias	This feasibility study is particularly vulnerable to attrition bias, given firstly its small sample size and secondly the fact that any remaining pool of participants may have a more positive opinion of the intervention, the assessments and general study participation, than those who withdraw. Combined, these factors may produce an unduly positive view of feasibility.	This bias is mitigated by efforts to collect data from all randomised participants, including those who withdraw or do not complete the interventions.
Centripetal bias	While this type of bias most readily affects effectiveness outcomes (which are not analysed in this study), it may still affect this study in two ways: 1. the location of the study (York, UK) is well-populated with practitioners of acupuncture and nutritional therapy and this may distort data on the feasibility of practitioner recruitment. 2. while participants are allocated to practitioners by the study, a change of practitioner before the first appointment is permitted (to accommodate preferences for location, previous relationship, etc), and this may distort data regarding attrition, particularly if coupled with some obsequiousness bias.	1. mitigated by an assessment of numbers of therapists and evaluation of reasons for non-participation, which may be applied to other study locations; 2. mitigated by the inclusion of questions in the follow-up questionnaire regarding relationship with practitioner, in order to detect the presence of bias.
Compliance bias	The interventions in this study constitute both therapy attendance and an associated programme of lifestyle advice. Compliant participants retained at follow-up may have a different view of the acceptability of interventions and overall study participation, which may not be generalisable to participants in a future trial.	To detect this, levels of compliance are self-reported in the assessment questionnaires.

Detection bias	In relation to this feasibility study, the evaluation of outcomes of group placement acceptability, intervention acceptability and study participation acceptability may be influenced by the participant's experience of treatment effects (or by lack of treatment for any participants affected by resentful demoralisation); and it is further known that the positive expectation of treatment is associated with a positive outcome (Eklund et al., 2019).	To determine the presence of potential detection bias, all participants are polled, pre-intervention, on their allocation satisfaction and their treatment expectation. The sample size is not large enough to detect any reliable associations, but this issue will be critically discussed in the thesis.

Dilution bias	Participants may choose to have private treatments in the study therapy to which they have not been assigned, or may choose to have other treatments in addition to the therapy to which they have been assigned.	This is detected by the inclusion of questions on the final follow-up questionnaire to detect this confounding factor.

Experimenter/ observer bias, perception bias and confirmation bias	The sole researcher/assessor is also a qualified acupuncturist which, in an open trial, may lead to confirmation biases including those associated with assessment of feasibility.	To mitigate this, verification sources are available against which outcomes may be checked, including recordings of all interviews; original completed questionnaires; and data from ambulatory ECG devices. In addition, a reflexive form of thematic analysis is used to analyse qualitative content, which prompts awareness and active mitigation of expectancy effects and confirmation/perception biases during qualitative data analysis. Participants will meet the researcher (online) during recruitment and assessments and may feel some loyalty to the study arising from their relationship with the researcher. This may delay or prevent attrition, giving rise to potential bias affecting the reliability of Objective 3 (reasons for participant retention). This is particularly important as the scale of a future trial would require a team of researchers, and therefore this bias would not be replicated. To assess the presence and effect of this bias in the feasibility study, participants are asked about any effect of loyalty in the three-month follow-up questionnaire.

Hawthorne effects and/or apprehension bias	Participants may experience and report unduly positive outcomes as a direct result of trial participation.	It is not possible to effectively mitigate these effects, as this is an open trial: no effective 'sham' version of nutritional therapy can be given, and acupuncture 'sham' treatments have been demonstrated to be clinically, if minimally, active.

Industry sponsorship bias	The study is part-funded by the British Acupuncture Council (BAcC), which may lead to some perceived systemic bias in favour of the study's acupuncture arm.	Outcomes are reported not in terms of effectiveness of a given arm, but in terms of feasibility of trial design for a future large-scale trial; this may be thought to reduce the influence of industry sponsorship bias.

Non-response bias	Some data may be missing (not at random) in questionnaires or polls; non-responders may differ characteristically from responders, and the absence of their data may introduce bias affecting feasibility outcomes.	To mitigate this, the researcher will check all questionnaires on collection from the participant's location. Missing data in questionnaires will be highlighted and participants will be asked to supply this. Missing data will be analysed using the last observation carried forward method.

Obsequiousness bias	Participants may report positively exaggerated effects of treatment due to a desire to please their practitioner (perhaps as a result of the patient-practitioner relationship developed during the intervention) or the researcher (with whom a "patient-practitioner relationship" may also have formed, as the researcher will carry out all assessments during the study). Alternatively, if participants have developed an antipathetic relationship with practitioner or researcher, this may result in negatively exaggerated outcomes. Obsequiousness bias may also delay or prevent attrition, or alternatively may lead to drop-out.	To mitigate this, the three-month follow-up questionnaire contains questions regarding any wish to please the practitioner or researcher. A letter sent to participants lost to follow-up will ask similar questions. However, there is a possibility that such questions will be avoided, or will not be answered accurately. This form of bias cannot be effectively mitigated in an open trial with a sole researcher/assessor.

Reporting bias and data-dredging bias	This form of bias may arise if the data is scrutinised and analysed for any possible positive outcomes, and/or if only positive outcomes are reported.	All pre-specified outcomes will be reported, thus avoiding bias from selective outcome reporting. This trial protocol has also been published in a trial registry (ISRCTN 13671984). As this is a feasibility study, some exploratory analyses (i.e., not pre-specified) may be undertaken regarding feasibility outcomes; however, any such analyses may be arguably more acceptable in a feasibility study as they would be used to inform the design of a future trial, rather than to test a hypothesis of effectiveness.

Recall bias	Many outcomes rely on participants' self-report, which may be misremembered; this may be a challenge in a future trial.	For the present study, those feasibility-related outcomes that may be affected by recall bias will be mitigated by assessments at baseline and three months being focused towards the most recent aspect of the trial experienced (enrolment aspects at baseline; therapy aspects at three months, immediately after intervention close).

Selection bias	See comment under Limitations, above.	In mitigation of possible selection bias, study population characteristics will be reported fully.

Volunteer bias	Willing participants in the Santé-AF feasibility study may have different characteristics from those of the AF population generally, and this may introduce bias in the assessment of feasibility outcomes.	Because the likelihood of volunteer bias increases as the rate of refusals increases, proportions of those approached will be compared with those willing and not willing to undergo screening; recommendations will be made for the future trial re. increasing screening numbers.

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