Full title of the study

Acupuncture in **a**ddition to **s**tandard conservative treatment for **o**veractive bladder; a feasibility trial for a randomised controlled study

Acronym
The **ACASO** study

Draft Research Protocol Version 1.1 25th July 2018

Research Reference Numbers

IRAS Number: 241138

Sponsors Number: 08725

CPMS ID: 38879

Funders Number: Project Code PRF/17/B17

Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

..../...../.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature: Date:

..../...../.....

Name: (please print):

.....

List of Abbreviations

APR – Annual Progress Report
CI – Chief Investigator
BOTOX – Botulinum A toxin
FPFV – First Patient First Visit
LPFV – Last Patient First Visit
FH – Freeman Hospital
ICECAP A - Icepop capability measure for adults
ICIQ – International consultation on incontinence questionnaire
MRC - Medical Research Council
NICE – National Institute for Health and Care Excellence
NuTH – Newcastle upon Tyne Hospitals
NIHR – National Institute for Health Research
OAB – Overactive bladder
PCPI – Patient, carer, and public involvement
PI – Principle Investigator
PIS - Patient Information Sheet
RCT – Randomised controlled trial
REC – Research Ethics Committee
RVI – Royal Victoria Infirmary
RDS NE – Research Design Service North East
SNS – Sacral nerve stimulation
SPSS – Statistical Package for the Social Sciences
UK – United Kingdom
3DBD – 3-day bladder diary

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Key Study Contacts

Chief Investigator	Emma Hargreaves Clinical Specialist Physiotherapist Physiotherapy Department Level 2 New Victoria Wing Royal Victoria Infirmary Queen Victoria Road Newcastle upon Tyne NE1 4LP 0191-2825484 emma.hargreaves@nuth.nhs.uk
Study Co-coordinator	As above
Sponsor	Newcastle upon Tyne Hospitals NHS Foundation Trust
Funder(s)	Chartered Society of Physiotherapy Charitable Trust
Key Protocol Contributors	Emma Hargreaves
Committee	Trial Steering Committee Members Emma Hargreaves Chief Investigator – details as above Dr. Carl Clarkson Academic supervisor Senior Lecturer Northumbria University Coach Lane Campus Coach Lane Benton Newcastle upon Tyne NE7 7XA 0191 2156113 carl.clarkson@northumbria.ac.uk Mr. Christopher Harding Medical advisor/Principle Investigator Consultant Urologist Freeman Hospital Freeman Road High Heaton Newcastle upon Tyne NE7 7DN 0191 28 chris.harding@nuth.nhs.uk

	Ms. Tracy Ord Nursing Advisor Uro-gynaecology Nurse Consultant Women's Health Unit Level 2 New Victoria Wing Royal Victoria Infirmary Queen Victoria Road Newcastle upon Tyne NE1 4LP 0191 28 tracy.ord@nuth.nhs.uk Ms. Julie Smith Patient representative juliesmith1@gmail.com Mobile number 07817684980

Study Summary

Study Title	**Ac**upuncture in **a**ddition to **s**tandard conservative treatment for **o**veractive bladder; a feasibility trial for a randomised controlled study
Internal ref. no. (or short title)	The ACASO study
Study Design	A two-group feasibility study
Study Participants	NHS patients referred to uro-gynaecology or urology departments with symptoms of overactive bladder syndrome
Planned Size of Sample	30
Follow up duration	14 weeks
Planned Study Period	2 years
Research Aims	To assess the feasibility of the study design in preparation for a larger treatment effect study (ACASO II)

Funding and Support in Kind

FUNDER	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
Chartered Society of Physiotherapy Charitable Trust	£25,000

Role of Study Sponsor and Funder

The Newcastle upon Tyne Hospitals NHS Foundation Trust will have overall responsibility for the initiation and governance of the study.

The Funder has reviewed the study design and requested three conditions be met. These have been incorporated into the study protocol.

A condition of funding is that the results will be presented at Physiotherapy UK – the profession's annual conference. Funds to facilitate this are provided by the funder over and above the grant award.

Role and Responsibilities of Trial Steering Committee (TSC)

The TSC will be made up of individuals with expertise in the clinical area and those actively involved in carrying out the study. It will also include a former patient to ensure the participants are represented.

The TSC will meet at 4 designated points during the study to

- Ensure compliance with protocol
- Monitor recruitment process and progress
- Review and respond to any adverse events
- Review and respond to any serious adverse events
- Review data collection
- Review data analysis
- Review results
- Plan dissemination of results

Protocol Contributors

- The sponsor will oversee all aspects of the study design and conduct. Sponsorship of the study will only be granted when all the study documents have been reviewed and accepted as fit for purpose.
- The protocol has been written by the CI and reviewed by the academic supervisor, the medical advisor and the Sponsors research staff

- Funds will not be released by the funder until ethical approval has been obtained.
- An outline of the study has been reviewed by the NIHR RDS NE consumer panel. Feedback has been received and this has guided the study design. A group of patients, who have the condition and received the intervention being studied, have reviewed the lay summary document and given feedback. Their views have been incorporated into the protocol.

Key Words:

Overactive bladder, acupuncture, standard treatment, feasibility study

Study Protocol

Acupuncture in **a**ddition to **s**tandard conservative treatment for **o**veractive bladder; a feasibility trial for a randomised controlled study

1 Background

Overactive bladder (OAB) is defined by the International Continence Society as urinary urgency with or without urgency incontinence, usually associated with frequency and nocturia[1]. The EPIC study[2] demonstrated that 11.8% of the population had symptoms of OAB, and that OAB was the most reported complaint of lower urinary tract symptoms (LUTS) affecting men (10.8%) and women (12.8%) This is equivalent to one in six of the UK population. An earlier study[3] found a larger prevalence for individuals over the age of 40 years (16.6%), which increased with age. This equates to approximately 10 million individual sufferers in the United Kingdom (UK). In addition, OAB is associated with anxiety and depression[4] 27% of people with OAB had depression using the Hospital Anxiety and Distress Scores (HADS >8), which was more than age matched controls without OAB. OAB has been associated with distress and social isolation[5].

The National Overactive Bladder Evaluation Programme (NOBLE)[5] estimated that the cost of treating OAB in the United States was $12.02 billion in 2000, which was comparable to the cost of treating osteoporosis or breast cancer[5].

OAB symptoms could result from multiple causes. Three possible mechanisms are discussed by Michel and Chapple[6]. These include:

- Alterations at the level of the sensory signals originating in the afferent bladder nerves, (sensory urgency).
- Alterations in efferent nerve signals (motor urgency)
- A possible malfunction of the smooth muscle itself (known as myogenic theory).

Current evidence is not sufficient to promote one theory over the others and it is possible that all three mechanisms are influential.

Current treatments for OAB include:

- The use of botulinum toxin A (Botox) injections into the detrusor muscle of the bladder wall. This involves admission to hospital and may require repeated treatments. It is associated with a risk of urinary retention requiring intermittent self catherisation and urinary tract infection[7].

- Implanted sacral nerve stimulation (SNS), where a permanent stimulator is placed within the body to stimulate the sacral nerves. This is a costly procedure requiring in-patient care and repeated follow up, and is associated with loss of efficacy, and a need for subsequent operations[7].
- Medications are frequently prescribed for OAB, with first choice medications being anti-cholinergic agents such as Oxybutynin, Tolteradine and Solifenacin[8]. These agents affect the efferent control of the detrusor muscle by antagonising the cholinergic muscarinic receptor[8]. However, these drugs can cause adverse effects, including dry mouth, constipation and have recently been associated with an increased risk of developing dementia[9]. Three Cochrane reviews have established the evidence for treatment and recommendations for prescribing[8,10&11] and establish the role of medication in the treatment of OAB. However, the rate of discontinuation of medication by patients is a concern. A study[12] of compliance with 6690 patients in the over 65's population reported only 11.4% were compliant after 6 months of treatment with Oxybutynin. A later study[13] of 2496 patients found that only 4.8% of participants were more than 80% compliant with their medication regime after 6 months of treatment. Reasons for discontinuing treatment were varied but 89% who had discontinued treatment felt that the medication was not meeting their expectations in terms of efficacy of symptom relief and incidence of side effects[13].

The National Institute for Health and Care Excellence guidance (NICE)[7] advocate conservative treatment that should consist of: education about bladder health; advice on reducing caffeine intake; weight reduction if BMI is greater than 30, and; a bladder re-training programme that lasts a minimum of six weeks. However, a systematic review[14] reported that despite these interventions being widely adopted, there is little high-quality research to support their efficacy.

Physiotherapists are becoming increasingly involved with OAB management, in which acupuncture is sometimes used. Abnormality of neural pathways and a failure of integrated function are thought to be a mechanism underlying OAB[15]. Subcutaneous needling in acupuncture can mediate the nervous system by sensory stimulation[16] and effect neurotransmitters[17]. It is postulated that acupuncture may have an effect on OAB symptoms via these mechanisms. Acupuncture has a low serious adverse event profile[18], and recently there has been a large RCT comparing acupuncture to Tolteradine which demonstrated that

both treatments had a similar effect on OAB symptoms[19]. A systematic review in 2016[15] concluded that "existing studies serve as a promising foundation to suggest a role for acupuncture in treating OAB". The review authors concluded further high-quality studies were required to establish treatment efficacy and cost effectiveness. There has not been a recent study comparing the effectiveness of conservative measures with acupuncture. If treatment efficacy can be demonstrated this will allow a discussion of where, in the treatment hierarchy, acupuncture may be most beneficial. Given that existing interventions such as medication have poor compliance rates, further study of acupuncture effectiveness is warranted. Medical Research Council (MRC)[20&21] and CONSORT[22&23] stipulate that prior to investigating effectiveness, thorough feasibility testing should be conducted. The ACASO study is a step to achieving this aim

To ensure this study is fit for purpose, clinicians and academics with a wide range of experience in women's health, urology, acupuncture and research activity have given advice on the proposal. In addition, a group of patients with experience of OAB have provided vital patient, carer and public involvement (PCPI). The consumer panel at NIHR Research and Design Service North East (NIHR RDS NE) has given feedback on the proposal which has resulted in alterations to the study protocol. The study will be based at The Newcastle upon Tyne NHS Foundation Trust (NUTH) which has an excellent reputation in relation to research activity and has a support structure for AHP clinical research. The Clinical Trials Unit at the Trust has been consulted on this proposal and has given advice on aspects of this feasibility study. This relationship will be developed when planning the ACASO II study.

The ACASO study has been awarded a small grant of £25,000 by the Chartered Society of Physiotherapy Charitable Trust, following peer review of the proposal. The proposal and study protocol have been reviewed by an academic supervisor and medical advisor.

2 The future definitive trial: ACASO II

The objective of ACASO II is to address the question whether acupuncture, in addition to standard conservative care, gives greater symptom relief in patients with OAB, when compared to standard conservative care alone. Where the feasibility, patient acceptability, and parameters to inform a power calculation are lacking for a definitive trial, a well-designed feasibility study is required[24]. In the ACASO study we will test protocol procedures,

patient recruitment and retention rates, consent processes, randomisation, patient acceptability, and collect data to power ACASO II. The ACASO II study is not being put forward for ethical consideration at this point.

3 Research Methods/Design

3.1 Aim

In line with recommendations for feasibility studies from CONSORT[21&22], this study will explore the practicalities of delivering acupuncture for urinary symptoms secondary to overactive bladder syndrome, through an assessment of the following:

3.2 Primary objectives

The primary objectives are to demonstrate that:

- Recruitment is possible
- To gauge participants acceptance of being part of the study using the study exit questionnaire (Appendix 5)
- To measure the acceptability of the outcome measures:
    - A three-day bladder diary[25] (3DBD)
    - The International Consultation on Incontinence Questionnaire[26] (ICIQ)
    - ICEpop CAPability measure for Adults[27] (ICECAP A)

See Appendix 5 for copies of the outcome measures

- Assess the length of time take to complete recruitment

These measures will inform the design of ACASO II and give insight into the practicality of delivering the intervention in a clinical setting.

3.3 Secondary Objectives

To analyse the treatment outcome measures to identify trends in the data and allow sample size calculation for the ACASO II study.

3.4 Design

This is a single centre feasibility study involving NHS patients with overactive bladder symptoms. The study employs a two-group design comparing current standard care with

standard care plus acupuncture. Participants will be randomly assigned to a group using an online service. A total of 30 participant are required, 15 in each group. Participants will be involved in the study for a total of 12 weeks. The three outcome measures will be completed at three separate time points during the study – at the first intervention, at 8 weeks after entering the study and at 14 weeks after entering the study.
The participant study experience will be studied by means of an exit questionnaire.

3.5 Study setting

The study will be based at the Newcastle upon Tyne Hospitals NHS Foundation Trust. The participants will be recruited from patients referred to the out-patient gynaecology and urology clinics complaining of symptoms of OAB.

3.6 Recruitment

Inclusion criteria

- Patients with a clinical diagnosis of idiopathic OAB syndrome
- Absence of other active urinary symptoms
- Willingness to take part in the study protocol
- Ability to complete outcome measures
- Ability to give informed consent.
- Acupuncture not contra-indicated i.e. no history of unstable heart conditions, unstable epilepsy or diabetes, bleeding disorders.

Exclusion criteria

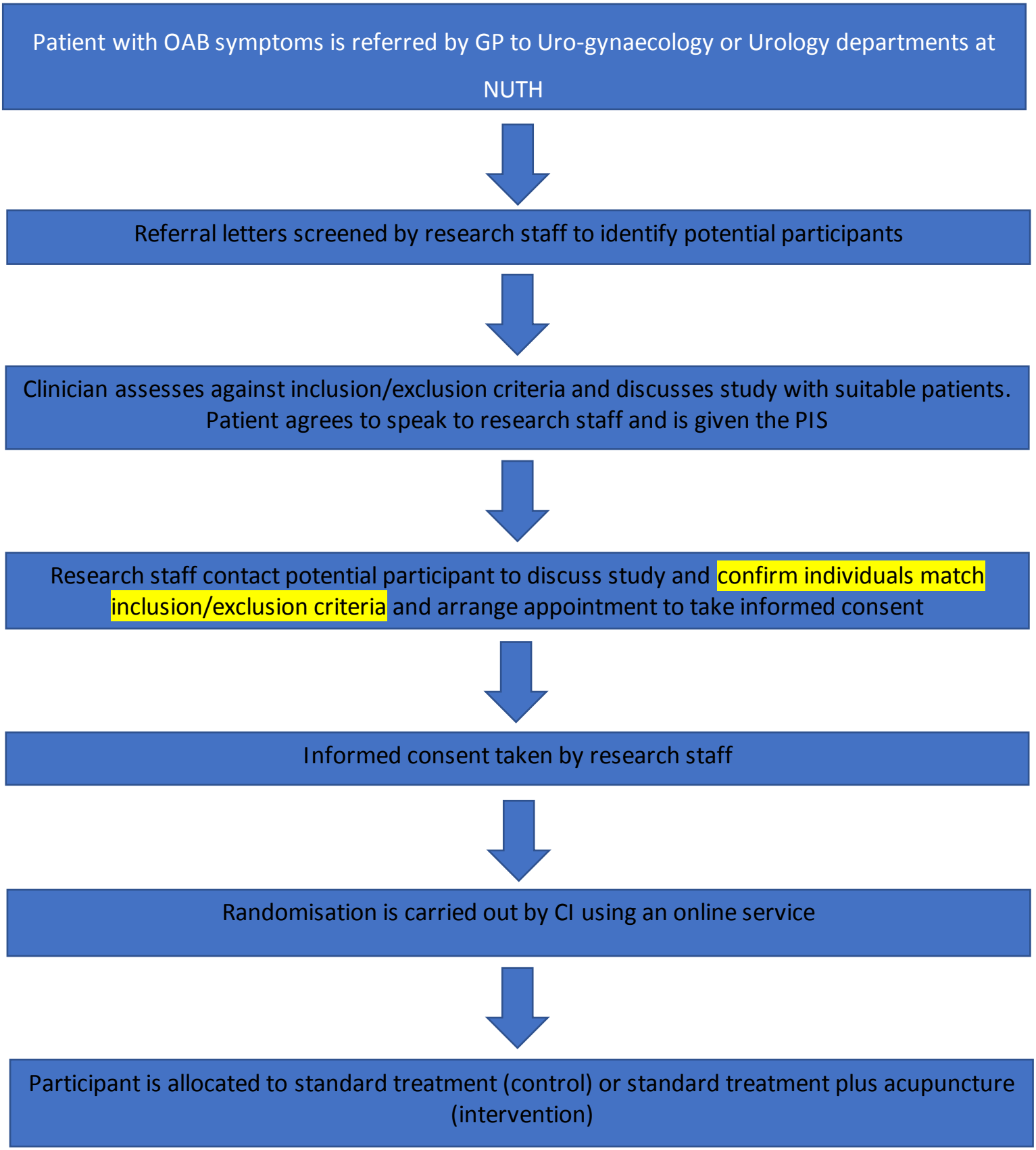
- Evidence of other pathology that may be contributing to OAB symptoms i.e. urinary tract infection or a neurological condition. Treatment specific for these conditions should be offered to individuals
- Pregnancy - transient urinary symptoms can be present during pregnancy and often resolve spontaneously following delivery. There are some acupuncture points that are contraindicated in pregnant women
- Unable to comprehend and retain the trial information i.e. poor understanding of English - the cost of employing interpreters to facilitate inclusion of patients who do not speak fluent English is beyond the financial scope of this feasibility study

Screening

Potential participants will be identified by research staff from GP referral letters to uro-gynaecology and urology clinics. A study alert form (Appendix 1) will be placed on the patient's notice, reminding the clinicians seeing the patient to assess eligibility to enter the study. The clinician will identify if the patient matches the inclusion/exclusion criteria and document this on the alert form. The clinician will discuss the study with the patient and ask if they would like to take part. If they are interested in participating, the clinician will document their preferred form of communication (telephone or email) and give the patient the Patient Information Sheet. The alert form will be collected from clinic by research staff and passed to the CI.

A member of the research team will contact the potential participant within one working week to discuss the study, answer any questions, confirm that the potential participant meets the inclusion/exclusion criteria, and arrange an appointment to take consent.

Recruitment flow chart



3.7. Consent

Potential participants in the study will give informed consent prior to inclusion by the following means.

- The study will be introduced by a clinician and written information on the study will be provided
- There will be time to consider participation and an opportunity for the potential participant to ask questions prior to entering the study
- All potential participants will be screened by research staff using the criteria below to ensure they have capacity to give informed consent
    - understand the purpose and nature of the research
    - understand what the research involves, its benefits (or lack of benefits), risks and burdens
    - understand the alternatives to taking part
    - be able to retain the information long enough to make an effective decision.
    - be able to make a free choice
    - be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity)
- Written informed consent will be taken at the first study visit prior to the first intervention. Permission will be sought to inform the participant's GP that they are entering the study (Appendix 2). A study inclusion form will be filed in the participants medical notes (Appendix 3). If the participant decides not to enter the study or is deemed unable to give informed consent, the first intervention is standard treatment so there will be no delay in receiving care caused by the study consent procedure.

4 Trial Proceedures

4.1 Randomisation

Once informed consent has been taken, the participant will be randomly assigned to a group using an online randomisation service from sealedenvelope.com[28]. Once logged into website the participants study ID is typed into the system, and they are randomly assigned to group A (standard care) or group B (standard care plus acupuncture). The result of the randomisation will be emailed to the CI. This process will be undertaken by the CI. Participants will be informed which group they are in. If they are in the acupuncture group, arrangements for acupuncture treatment will be made with the participant at this point.

4.2 Blinding

Due to the nature of the interventions it is not possible to blind participants regarding the type of treatment they will receive. As the aim of this study is feasibility this is acceptable. It may be necessary to employ the use of a sham acupuncture procedure when considering the design of ACASO II.

4.3. Primary Outcomes

- Participants' willingness to enter the trial – measured by the ratio between those who consented to participate and those who were eligible and approached
- Participants acceptability of study design – measured by the completion rate of participants in each group and the degree of completeness of the three outcome measures selected (3DBD, ICIQ, and ICECAP A – Appendix 4)
- Study experience questionnaire – this is an opportunity for participants to give feedback on their experience of the study. It will be analysed for themes that may inform the design of ACASO II.
- Participant recruitment rate – measured by the number of patients randomised divided by the recruitment period. The recruitment period is defined as the date of the first patient first visit (FPFV) until the last patient first visit (LPFV). Anticipated recruitment rate is 2 per month giving a projected recruitment period of 15 months to recruit 30 participants.

4.4 Secondary Outcomes

The treatment outcome measures will be analysed to identify trends in the data and be used to calculate sample size requirement so for ACASO II.

4.5 Interventions

Standard Care (Control)

Participants will be asked to complete a 3-day bladder diary prior to their first study visit and bring this with them when they attend (asper standard care). Research staff will ask the participant to complete the ICIQ and ICECAP A measures after taking consent.

The care given by the specialist nurse will be guided by NICE guideline 171[7] which recommends the following lifestyle and behavioural interventions:

- Review of 3-day bladder diary
- Modification of high or low fluid intake
- Reduction of caffeine intake if relevant
- A bladder retaining programme
- Weight reduction if BMI is greater than 30

The specialist nurse will discuss these topics with the participant and suggest ways to improve their symptoms of OAB. The participant is at liberty to choose whether they put this advice into action. Standard care will be delivered during a 30-minute appointment in the Women's Health Unit at the RVI. A letter detailing the intervention will be written and sent to the participant's GP and a copy will be placed in the medical notes as per standard practice. A second appointment will be arranged for 8 weeks (+/- 7 days) following the first appointment to review progress. The participant will be asked to complete a second 3-day bladder diary prior to this appointment and research staff will complete the ICIQ and ICECAP A measures with them during the 2nd visit.

The third set of outcome measures will be sent to the participant by research staff at week 14 along with the exit questionnaire – they will be asked to complete these at home and return to the CI in a prepaid envelope.

Acupuncture group (Intervention)

This group will receive the same standard care documented above and in addition will have 6 treatments of acupuncture based on western acupuncture principles[29]. If possible the 1st and 6th acupuncture treatments will coincide with the standard care appointments to minimise the need for repeated study visits.

All acupuncture treatments will take place in the Women's Health physiotherapy department at the RVI. All participants will receive acupuncture in accordance with the standard operating policy detailed in Appendix 5. A record of the treatment will be recorded using the acupuncture treatment form (Appendix 6) and stored in the participants physiotherapy record.

4.6 Study Assessments Table 1 – Standard treatment group

Assessment	Screening	Prior to 1st visit	1st visit Day 0	Prior to 2nd visit	2nd visit Week 8	Week 14
Identification of potential participants	x					
3-day bladder diary*		x		x		x
Consent taken			x			
Randomisation			x			
ICIQ			x		x	x
ICECAP A			x		x	x
Standard Treatment			x		x	
Monitoring of Adverse Events			x		x	x
Monitoring of Serious Adverse Events			x		x	x
Exit questionnaire						x

*****as per standard care

4.7 Study Assessments Table 2– Standard treatment plus acupuncture group

Assessment	Screening	Pre-visit 1	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Pre-visit 6	Visit 6	Week 14
Identify participants	x									
3-day bladder diary*		x						x		x
Consent taken			x							
Randomisation			x							
ICIQ			x						x	x
ICECAP A			x						x	x
Standard Treatment			x						x	
Acupuncture Treatment			x	x	x	x	x		x	
Monitoring of Adverse Events			x	x	x	x	x		x	x
Monitoring of Adverse Events			x	x	x	x	x		x	x
Exit Questionnaire										x

*as per standard care

5. Data Collection and outcome measures

The following proceedures and assessments will be carried out in accordance with the study schedule detailed in tables 1&2.

- Written informed consent
- Randomisation
- Completion of outcome measures: 3DBD, ICIQ, ICECAP A
- Standard treatment for OAB symptoms
- Acupuncture treatment
- Documentation of adverse and serious adverse events
- Exit Questionnaire

5.1 Recruitment data

Data collection	Method	By Whom	How recorded	Frequency
Number of patients with OAB symptoms in clinic	Review of GP referral letters before the clinic	Research staff	Spreadsheet	Weekly
Number of patients who fit inclusion criteria	Discussion with patient	Clinician/ Research staff	Form attached to notes – collected at the end of clinic session Spreadsheet	Weekly
Number who consent to participate	Completed consent forms	Research staff	Spread sheet	Weekly
Number who complete all aspects of the study	Completed outcome measures	Research staff	Spreadsheet	Weekly
Attrition rate	Failure to attend appointments/ complete outcome measures	Research staff	Spreadsheet	Weekly
Reasons for attrition	Discussion with participant	Research staff	Spreadsheet	Weekly

5.2 Outcome measure data

Measure	When collected	By whom	How recorded	Analysed using
3 Day Bladder Diary	Baseline, 8 weeks and 14 weeks	Research staff	Spreadsheet	SPSS
ICIQ	Baseline, 8 weeks and 14 weeks	Research staff	Spreadsheet	SPSS
ICECAP A	Baseline, 8 weeks and 14 weeks	Research Staff	Spreadsheet	SPSS

5.3 Participant experience data

Data will be analysed to identify themes and will be used to inform the design of ACASO II.

5.4 Data handling and record keeping

All investigators and study site staff will comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Caldicott principles will be applied to all data collected as part of the study. All study team members are governed by a duty of confidentiality as stated in their terms of employment by NuTH.

Personal data held as part of the study will be protected by:

- The creation of coded, depersonalised data where the participant's identifying information is replaced by an unrelated sequence of characters.
- The CI is the only team member with access to both the data and the linking code. These files will be kept in separate locations using encrypted digital files within password protected folders.
- No participant identifiable data will leave the study site.
- Site files and paper records will be kept in a locked filing cabinet in a room only accessible by a keypad.
- Paper records created as part of a treatment record will be kept for 7 years in line with NuTH policies.
- Emma Hargreaves is the Caldicott Guardian for the study

5.5 Submission of accrual data to the UK Clinical Research Network

This study will apply for adoption to the NIHR Portfolio. Accrual data will be submitted on a monthly basis, by research staff, in accordance with NIHR Clinical Research Network guidelines.

5.6 Study withdrawal

Participants may withdraw from the study at any time without giving a reason. The investigator may also withdraw patients from the study in the event of illness, adverse events, serious adverse events, suspected unexpected serious adverse reactions, protocol violations or administrative or other reasons. Participants who withdraw will be asked if they would be willing to provide follow-up data collected as per the study protocol. Participants withdrawn from the study will not be replaced. Participants will be asked if they are willing to give reasons for withdrawal, as these may be pertinent to the study design and so inform the design of ACASO II. Participants do not have to comply with this request. The PIS reflects this request.

6 Statistical Analysis

The feasibility data produced during the study will be analysed using descriptive statistics. Inferential statistics will be used to analyse the outcome measures data and the Mann Whitney U test will be applied to this data using SPSS.

6.1 Sample Size Calculation

No formal sample size calculation has been performed for this study as the primary outcome measures are concerned with feasibility, studying the recruitment to and randomisation of the trial, and the acceptability of the trial in this population of patients. It has been suggested that a minimum of 12 participants per group is an adequate number to give "precision around the estimates to be used to design future studies"[30]. It is anticipated that some participants may not complete the full study process so a recruitment target of 15 in each group would allow for attrition of 20%. Two previously published studies[19&31] demonstrated attrition rates of 13% and 10% respectively, therefore a planned 20% attrition rate should allow adequate numbers to give meaningful data for analysis. It is estimated there are 12 new patients per week presenting with OAB symptoms in the two clinics

identified for recruitment. This gives a possible pool of 720 patients during the 60-week recruitment period.

7 Ethical and Regulatory Considerations

7.1 Assessment and management of risk

Potential Risks Identified

Standard treatment

- Embarrassment regarding discussion of incontinence
- Questions that participants may find intrusive
- May require lifestyle changes that impact on patient's current habits

Acupuncture treatment

Documented side effects include:

- Pain on needle insertion
- Minor bleeding on needle removal
- Dizziness
- Nausea and/or vomiting,
- Fainting
- Headache
- Tiredness

There are some reports of serious adverse effects following acupuncture[32], these include:

- Infection
- Pneumothorax
- Puncture of internal organs
- Death has been reported in 2 cases of severe infection

Management Plan to minimise risks

- Experienced clinical staff who have an empathetic approach and extensive knowledge of the condition and management strategies will deliver the interventions
- Acupuncture side effects usually resolved by removing needles and discontinuing treatment
- Participants will be closely monitored during acupuncture sessions by a physiotherapist fully trained and experienced in acupuncture practice
- A standard operating policy will be used to maintain participant safety during acupuncture treatment (Appendix 5)

- Any AEs or SAEs will be reported and discussed at the TSC

7.2 Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study, a favourable opinion will be sought from the UK Health Departments Research Ethics Service. Following the REC proceedure the following will apply to this study:

- Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site.
- All correspondence with the REC will be retained.
- The CI will produce the annual reports as required.
- The CI will notify the REC of the end of the study.
- An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.

7.3 Peer review

The study has been reviewed by the Scientific Panel of the funding body. Three conditions were set as a result of this review and these amendments have been incorporated into the protocol and approved by the funder.

7.4 Patient & Public Involvement

The initial study protocol has been reviewed by the NIHR RDS NE consumer panel based at Newcastle University. Feedback was received from the panel and their suggestions have been incorporated in to the protocol with particular reference to improving the participant experience during the study and reducing the burden of participation. A group of current and former patients who have experience of OAB symptoms and treatment with acupuncture were asked to give feedback on the lay summary document and in particular give an opinion on the research question and its relevance. This was overwhelmingly positive, and a former patient has agreed to act as a patient representative on the trial steering committee.

Study participants, current and former patients who have experienced the acupuncture intervention and members of the consumer panel who gave feedback on the proposal will be invited to an event to publicise the results of the study once they have been collated.

7.5 Protocol compliance

- Accidental protocol deviations will be reported to the CI and discussed at the TSC. Protocol deviations will be a standing item on the TSC agenda.
- Deviations from the protocol which are found to frequently recur will require immediate action. Any instance of recurrent deviations will be highlighted and discussed at the TSC. If appropriate an amendment to the protocol may be sought from the REC.

7.6 Indemnity

- NHS indemnity will meet the potential legal liability of the sponsor for harm to participants arising from the management of the research
- NHS indemnity will meet the potential legal liability of the sponsor for harm to participants arising from the design of the research
- NHS indemnity will meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research
- There is no provision for payment of compensation in the event of harm to the research participants where no legal liability arises

7.7 Access to the final study dataset

- The final data set will not contain any personally identifiable information and will only be available to the CI and TSC.
- The study will allow site investigators to access the full dataset if a formal request describing their plans is approved by the TSC.
- It is not envisaged that that dataset will be used for secondary analysis

8 Dissemination

8.1 Dissemination policy

- The dataset created in the study is the property of Newcastle upon Tyne Hospitals Foundation NHS Trust
- On completion of the study, the data will be analysed and tabulated and a Final Study Report (FSR) prepared.
- The full study report can be accessed by contacting the CI.
- The results of the study will be presented at Physiotherapy UK and submitted for publication in peer reviewed journals.
- A presentation of the results will be held for all study participants and members of the public that have assisted with the design and conduct of the study.

8.2 Authorship eligibility guidelines and any intended use of professional writers

The authors of the protocol are:

- Emma Hargreaves – Chief Investigator
- Carl Clarkson – Academic supervisor
- Chris Harding – Medical Advisor/Principle Investigator
- Nicola Adams - Statistician

9 References

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Appendices

Appendix 1	Screening Tool
Appendix 2	Letter to GP
Appendix 3	Notification for Medical Records
Appendix 4	Outcome measures • 3DBD • ICIQ • ICECAP A • Exit Questionnaire
Appendix 5	Acupuncture Standard Operating Proceedure
Appendix 6	Acupuncture Treatment Record

Appendix 1 Screening Tool **Clinic date:**

Review of GP Referral letter	Symptom present
Urinary urgency	
Urinary Frequency	
Nocturia	
Urinary Incontinence	

Screened by:

Eligibility

<table>
<tr><th>Inclusion criteria</th><th>Y/N</th><th>Exclusion criteria</th><th>Y/N</th></tr>
<tr><td>OAB symptoms</td><td></td><td>Other pathology likely to contribute to OAB symptoms i.e. infection/neurological condition</td><td></td></tr>
<tr><td>No other urinary symptoms i.e. UTI</td><td></td><td>Pregnancy</td><td></td></tr>
<tr><td>Not taking medication for OAB</td><td></td><td>Unable to comprehend/retain trail information i.e. poor understanding of English, dementia</td><td></td></tr>
<tr><td>Willing to take part in study</td><td></td><td colspan="2" rowspan="8">Please circle:
Study Discussed: Y / N

Potential participant: Y / N

PIS supplied: Y / N

Willing to discuss with CI: Y / N

Name:
Preferred contact method: Telephone / email

Contact: Telephone number:

Email address:</td></tr>
<tr><td>Able to complete 3DBD and 2 questionnaires</td><td></td></tr>
<tr><td>Able to consent</td><td></td></tr>
<tr><td>Acupuncture not contraindicated</td><td>Y/N</td></tr>
<tr><td colspan="2">Unstable heart disease
Unstable epilepsy
Unstable diabetes
Abnormal blood clotting
Lymphoedema
Poor skin condition
Metal allergy
Caution – pacemaker</td></tr>
</table>

Completed by: **Signature:**

Appendix 2 GP Letter

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

GP Name and Address

Dear Dr

Your patient:

Address:

DOB:

NHS:

(Participant name) has agreed to take part in the study detailed below.

Acupuncture in **a**ddition to **s**tandard conservative treatment for **o**veractive bladder; a feasibility trial for a randomised controlled study

Acronym: The ACASO study

A 2 group comparative study to address feasibility. It will recruit 30 participants from outpatient Urology and Uro-gynaecology clinics at Newcastle upon Tyne Hospital Foundation NHS Trust (NuTH) with symptoms of Overactive Bladder (OAB). The participants will be randomly assigned to one of 2 groups.

- Standard conservative treatment - delivered by uro-gynaecology specialist nurses
- Standard conservative treatment plus six weekly acupuncture treatments provided by qualified physiotherapist trained and experienced in the delivery of acupuncture

Outcome measures

Participants will be asked to complete the following measures at the start of treatment, after 8 weeks of treatment, and 14 weeks after starting treatment

- A three day bladder diary
- ICIQ-SF
- ICECAP-A

In addition at 14 weeks after starting treatment, participants will be asked to complete a study exit questionnaire to capture information on their experience of taking part in the study.

The study is funded by the Chartered Society of Physiotherapy Charitable Trust and it is sponsored by Newcastle upon Tyne Hospitals Foundation NHS Trust. This study has been read and passed favourably by the North East – Newcastle & North Tyneside 1 Research Ethics Committee. It will form the basis of my Doctor of Philosophy thesis.

If you wish to have more information on the study a full protocol is available, please contact me – details below.

Yours Sincerely

(Signature)

Emma Hargreaves

Clinical Specialist Physiotherapist

Chief Investigator The ACASO study

Physiotherapy Department

Level 2 New Victoria Wing

Royal Victoria Infirmary

Newcastle upon Tyne

NE1 4LP

Telephone 0191 2825484

Email emma.hargreaves@nuth.nhs.uk

Appendix 3

Study Inclusion Form

Place patient identification sticker here

The above has agreed to be entered into the ACASO study

Study ID number: 08725

Date:

Signed:

Designation:

Appendix 4
Outcome measures

(on headed paper)

3-day Bladder diary

Please complete this diary over 3 consecutive days. If you work outside the home you should try to include at least one working day and at least one 'day off' or weekend day. We would like you to measure the amount each time you pass urine, by using a jug; if this is not possible, e.g. if you are away from home, please estimate the amount as small (✓), medium (✓✓) or large (✓✓✓); if you have any accidental leaks you should record these in the same way.
The 'sample' line at the top shows you how to use the diary.

Start Date:

Time	Drinks What kind	How much	Visits to bathroom How many urine Timers	How much (ml. fl.ozs or (✓)	Accidental Leaks How much? (✓)	Did you feel a strong urge? Circle as appropriate		What were you doing at the time? Sneezing, exercising Having sex, lifting etc
Sample	Coffee	1 mug	✓✓	250,200	sml med lge ✓✓	Yes	No	running
6-7 am						Yes	No	
7-8 am						Yes	No	
8-9 am						Yes	No	
9-10 am						Yes	No	
10-11 am						Yes	No	
11-12noon						Yes	No	
12-1pm						Yes	No	
1-2 pm						Yes	No	
2-3 pm						Yes	No	
3-4 pm						Yes	No	
4-5 pm						Yes	No	
5-6 pm						Yes	No	
6-7 pm						Yes	No	
7-8 pm						Yes	No	
8-9 pm						Yes	No	
9-10 pm						Yes	No	
10-11 pm						Yes	No	
11-12 Midnight						Yes	No	
12-1 am						Yes	No	
1-2 am						Yes	No	
2-3 am						Yes	No	
3-4 am						Yes	No	
4-5 am						Yes	No	
5-6 am						Yes	No	
24 hour total						Number of pads used today		

24 hour totals (for office use)

How many visits to the bathroom	Daytime ☐☐ Night time ☐☐	17-20
How much urine	☐ ml ☐☐☐ fl.oz No of	21-29
Accidental leaks (No. of episodes)	Small Medium Large	30-37
Number of pads		38-39

Start Date:

Time	Drinks What kind How much		Visits to bathroom How many urine Timers	How much (ml. fl.oz or ()	Accidental Leaks How much? ()	Did you feel a strong urge? Circle as appropriate		What were you doing at the time? Sneezing, exercising Having sex, lifting etc
Sample	Coffee	1 mug		250,200	sml med lge	Yes	No	running
6-7 am						Yes	No	
7-8 am						Yes	No	
8-9 am						Yes	No	
9-10 am						Yes	No	
10-11 am						Yes	No	
11-12noon						Yes	No	
12-1pm						Yes	No	
1-2 pm						Yes	No	
2-3 pm						Yes	No	
3-4 pm						Yes	No	
4-5 pm						Yes	No	
5-6 pm						Yes	No	
6-7 pm						Yes	No	
7-8 pm						Yes	No	
8-9 pm						Yes	No	
9-10 pm						Yes	No	
10-11 pm						Yes	No	
11-12 Midnight						Yes	No	
12-1 am						Yes	No	
1-2 am						Yes	No	
2-3 am						Yes	No	
3-4 am						Yes	No	
4-5 am						Yes	No	
5-6 am						Yes	No	
24 hour total						Number of pads used today		

24 hour totals (for office use)

How many visits to the bathroom	Daytime		Night time	
How much urine	ml		fl.oz	No of
Accidental leaks (No. of episodes)	Small	Medium	Large	
Number of pads				

Start Date:

Time	Drinks What kind	How much	Visits to bathroom How many urine Timers	How much (ml. fl.oz or ()	Accidental Leaks How much? ()	Did you feel a strong urge? Circle as appropriate		What were you doing at the time? Sneezing, exercising Having sex, lifting etc
Sample	Coffee	1 mug		250,200	sml med lge	Yes	No	running
6-7 am						Yes	No	
7-8 am						Yes	No	
8-9 am						Yes	No	
9-10 am						Yes	No	
10-11 am						Yes	No	
11-12noon						Yes	No	
12-1pm						Yes	No	
1-2 pm						Yes	No	
2-3 pm						Yes	No	
3-4 pm						Yes	No	
4-5 pm						Yes	No	
5-6 pm						Yes	No	
6-7 pm						Yes	No	
7-8 pm						Yes	No	
8-9 pm						Yes	No	
9-10 pm						Yes	No	
10-11 pm						Yes	No	
11-12 Midnight						Yes	No	
12-1 am						Yes	No	
1-2 am						Yes	No	
2-3 am						Yes	No	
3-4 am						Yes	No	
4-5 am						Yes	No	
5-6 am						Yes	No	
24 hour total						Number of pads used today		

24 hour totals (for office use)

How many visits to the bathroom	Daytime		Night time	
How much urine		ml	fl.oz	No of
Accidental leaks (No. of episodes)	Small	Medium	Large	
Number of pads				

ABOUT YOUR OVERALL QUALITY OF LIFE

Please indicate which statements best describe your overall quality of life at the moment by placing a tick (✓) in **ONE** box for each of the five groups below.

1. Feeling settled and secure

I am able to feel settled and secure in **all** areas of my life	4
I am able to feel settled and secure in **many** areas of my life	3
I am able to feel settled and secure in **a few** areas of my life	2
I am **unable** to feel settled and secure in **any** areas of my life	1

2. Love, friendship and support

I can have **a lot** of love, friendship and support	4
I can have **quite a lot** of love, friendship and support	3
I can have **a little** love, friendship and support	2
I **cannot** have **any** love, friendship and support	1

3. Being independent

I am able to be **completely** independent	4
I am able to be independent in **many** things	3
I am able to be independent in **a few** things	2
I am **unable** to be at all independent	1

4. Achievement and progress

I can achieve and progress in **all** aspects of my life	4
I can achieve and progress in **many** aspects of my life	3
I can achieve and progress in **a few** aspects of my life	2
I **cannot** achieve and progress in **any** aspects of my life	1

5. Enjoyment and pleasure

I can have **a lot** of enjoyment and pleasure	4
I can have **quite a lot** of enjoyment and pleasure	3
I can have **a little** enjoyment and pleasure	2
I **cannot** have **any** enjoyment and pleasure	1

Please ensure you have only ticked **ONE** box for each of the five groups.

ICECAP-A measure V2

☐☐☐☐☐☐☐☐ Initial number

ICIQ-UI Short Form

CONFIDENTIAL

☐☐ ☐☐ ☐☐ DAY MONTH YEAR

Today's date

Many people leak urine some of the time. We are trying to find out how many people leak urine, and how much this bothers them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

1 Please write in your date of birth: ☐☐ ☐☐ ☐☐ DAY MONTH YEAR

2 Are you *(tick one)*: Female ☐ Male ☐

3 How often do you leak urine? *(Tick one box)*

never ☐	0
about once a week or less often ☐	1
two or three times a week ☐	2
about once a day ☐	3
several times a day ☐	4
all the time ☐	5

4 We would like to know how much urine <u>you think</u> leaks.
How much urine do you <u>usually</u> leak (whether you wear protection or not)?
(Tick one box)

none ☐	0
a small amount ☐	2
a moderate amount ☐	4
a large amount ☐	6

5 Overall, how much does leaking urine interfere with your everyday life?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

ICIQ score: sum scores 3+4+5 ☐☐

6 When does urine leak? *(Please tick all that apply to you)*

never – urine does not leak	☐
leaks before you can get to the toilet	☐
leaks when you cough or sneeze	☐
leaks when you are asleep	☐
leaks when you are physically active/exercising	☐
leaks when you have finished urinating and are dressed	☐
leaks for no obvious reason	☐
leaks all the time	☐

Thank you very much for answering these questions.

(On Headed paper)
ACASO Study Exit Questionnaire

STUDY ID: **DATE:**

This questionnaire is designed to capture your experience of taking part in the ACASO study. We would welcome your honest feedback, be it positive or negative. It is our intention to apply for money to run a large study on several sites to investigate the treatment effect of acupuncture for OAB symptoms. The study you have taken part in has been designed to test the processes that will be needed in the second study (ACASO II), so your feedback is vital in shaping ACASO II. We want to understand how it has felt to be involved, what has gone well and what you have not enjoyed. Please give as much detail as you feel necessary to explain your experience, continuing on a separate page if necessary.
Thank you very much for completing this questionnaire and for participating in the study.

Emma Hargreaves,
Chief Investigator – The ACASO study.

1. Why did you decide to take part in the ACASO study?

2. Overall what has been your experience of participating in the study?

3. Thinking about the 3 outcome measures – how easy was it to complete them and do you have any suggestions for making the process easier?

3-day bladder diary:

ICIQ questionnaire:

ICECAP A questionnaire:

4. Have you had any "out of pocket" expenses as a result of taking part in the ACASO trial?

5. If you have received acupuncture as part of your treatment, you will have been offered travel expenses due to the extra appointments you have had to attend at the RVI.

Have you claimed these expenses?

If you have claimed expenses, please can you comment on the ease of the process?

If you have not claimed expenses can you give a reason why not?

6.Is there anything else you would like to pass on to the research team about your experience of taking part in the ACASO study?

Appendix 5

Standard Operating Policy for Acupuncture during the ACASO trial.

The participant is asked to confirm verbally at the start of each visit

- That they are well and consent to acupuncture
- There have been no changes in their general health or medications which may affect their treatment

The participant is asked to undress sufficiently to allow the needles to be inserted.

Position for treatment– supine on a treatment couch with head raised and pillows as required ensuring comfort

Skin preparation – the skin where needles are to be inserted will be cleaned with an a Clinell alcoholic 2% chlorhexidine skin wipe

Acupuncture points - needles will be inserted at the following locations

Point	Location	Needle Depth (cun*)	Needle length	Needle Make	Unilateral /Bilateral
Conception Vessel 3	On the midline of the abdomen 4 cun inferior to the umbilicus and 1 cun superior to the pubic symphysis	1.5	40mm	HMD Europe Classic Plus	Unilateral
Conception Vessel 4	On the midline of the abdomen 3 cun inferior to the umbilicus and 2 cun superior to the pubic symphysis	1.5	40mm	HMD Europe Classic Plus	Unilateral
Conception Vessel 5	On the midline of the abdomen 2 cun inferior to the umbilicus and 3 cun superior to the pubic symphysis	1.5	40mm	HMD Europe Classic Plus	Unilateral
Stomach 25	On the abdomen 2 cun	1.5	40mm	HMD	Bilateral

	lateral to the umbilicus			Europe Classic Plus	
Spleen 9	On the medial side of the lower leg, in a depression in the angle formed by the medial condyle of the tibia and posterior border of the tibia	1.5	40mm	HMD Europe Classic Plus	Bilateral
Spleen 6	On the medial side of the lower leg, 3 cun superior to the prominence of the medial malleolus, in a depression close to the medial crest of the tibia	1.0	25mm	HMD Europe Classic Plus	Bilateral
Kidney 7	On the medial aspect of the lower leg, in the depression 2 cun superior to Kidney 3 on the anterior border of the Achilles tendon	1.0	25mm	HMD Europe Classic Plus	Bilateral
Kidney 3	In the depression between the medial malleolus and the Achilles tendon, level with the prominence of the medial malleolus	1.0	25mm	HMD Europe Classic Plus	Bilateral

DeQi - A sensation of DeQi** will be sought on insertion.

Duration of treatment – 30 minutes

Stimulation of needles – will be achieved by rotating the needle to achieve DeQi on needle insertion, at 10 minutes after insertion and at 20 minutes after insertion.

Needle removal – a non-sterile protective glove will be applied to the non-dominant hand. A cotton wool ball will be held in this hand in readiness. The acupuncture needles are removed with the dominant hand and disposed of in a sharps bin in the treatment room. The cotton wool ball is used to apply pressure to any bleeding points. Pressure is maintained until bleeding stops. The cotton wool and glove are disposed of in an orange bin for contaminated waste.

Treatment record – an acupuncture treatment record form (Appendix 7) will be completed for each treatment and stored in the study file in a secure location in the physiotherapy department.

Footnote – Acupuncture terms

***Cun** – is the measurement of depth of insertion of acupuncture needles. This measure varies between individuals as it is based on the width of the patient's thumb. One thumb width =1 cun.[33]

****DeQi** refers to the sensation appreciated by the patient on needle insertion; it has been described in the literature[34] as follows;

"Although it is difficult in fully clarifying its mechanisms and effects, DeQi still can be considered as an instant "sign" of acupuncture response of the patient and acupuncturist, which has a significant value in clinic and research."

Appendix 6
Acupuncture treatment record form

Study ID: **Date:**

Consent to Acupuncture:				
Any change in health status **Yes/ No** **Details:** **Other changes since last treatment:**				
Skin Swabbed				
Position for treatment	**Supine on treatment couch**			
Points used	**Size**	**Depth**	**DeQi Achieved**	**Unilateral/ bilateral insertion**
CV 3,4,5	**40mm**	**1.5cun**		**Unilateral**
ST 25	**40 mm**	**1.5cun**		**Bilateral**
SP 9	**40 mm**	**1.5cun**		**Bilateral**
SP 6	**25mm**	**1.0cun**		**Bilateral**
KI 7	**25mm**	**1.0 cun**		**Bilateral**
KI 3	**25mm**	**1.0cun**		**Bilateral**
Total Number of needles	**Inserted:**		**Removed:**	
Stimulation of needles	**At insertion, after 10 minutes & after 20 minutes**			
Duration of treatment	**30 minutes**			
Adverse Events:				
Serious Adverse Events:				

Signed: **Designation:** **Date:** **Time:**