Full title of trial	Improving the Assessment of Faecal Incontinence: which patient groups would benefit from assessment with Multiple Array Probe Leiden (MAPLe)? This is a student study as part of a Research MD
Short title	Assessment of Faecal Incontinence with MAPLe
Version and date of protocol	Version 1 29/01/19
Sponsor:	University College London (UCL)
Sponsor protocol number	119731
Funder (s):	UCL Ashford and St Peter's NHS Foundation Trust
Clinicaltrials.gov no:	Submitted a/w approval
Intervention:	Additional assessment of participants with faecal incontinence with MAPLe
Single site/multi-site:	Multi site

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Protocol Version History

Version Number	Date	Protocol Update Finalised By (insert name of person):	Reasons for Update
1	19/01/19	Rachael Weatherburn	Peer Review
2	13/02/19	Rachael Weatherburn	Following JRO review

Signatures

The Chief Investigator and the JRO have discussed this protocol. The investigator agrees to perform the investigations and to abide by this protocol.

The investigator agrees to conduct the trial in compliance with the approved protocol, the UK Data Protection Act (2018), the Trust Information Governance Policy (or other local equivalent), the current UK Policy Framework for Research, the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator	 12/2/19	
UCL	Signature	Date
Sponsor		13/02/19
Sponsor representative		
UCL	Signature	Date

Contents

List of abbreviations

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
FI	Faecal Incontinence
MAPLe	Multiple Array Probe Leiden
AUS	Anal Ultra Sound
HRAM	High Resolution Anal Manometry
ARP	Anorectal Physiology
EMG	Electromyography
sEMG	Surface Electromyogrphy
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ISF	Investigator Site File
MDT	Multi-Disciplinary Team
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee

1. Trial personnel

See protocol cover page for Chief Investigator and Sponsor contact details.

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2. Summary

Objectives:	Primary Objective: To determine the role of MAPLe in the assessment of Faecal Incontinence (FI) in defined patient groups. Secondary Objective: Identify which patient groups benefit from physiological testing with MAPLe and receive targeted treatment
Type of trial:	This is a multi-centre cohort study investigating FI
Trial design and methods:	The study will take place across two trusts with specialist pelvic floor services. Participants will be recruited via referrals for anorectal physiology (ARP) with symptoms of FI meeting the inclusion/exclusion criteria. Participants will complete incontinence and quality of life questionnaires, undergo routine ARP with high resolution manometry (HRAM) and anal ultrasound (AUS), and additional assessment with MAPLe. Each assessment will be performed in accordance with a standardised protocol. ARP results will be discussed at the local MDT, should treatment be offered, the participant will undergo further testing with MAPLe, if no treatment if offered participation is complete.
Trial duration per participant:	12 months
Estimated total trial duration:	18 months
Planned trial sites:	Multi-Site: University College London Hospitals (UCLH) Ashford and St Peter's NHS Foundation Trust (ASPH)
Total number of participants planned:	120

Main inclusion/exclusion criteria:	Inclusion: Symptoms of FI, aged over and including 18, capacity to consent, male/female. Exclusion: anal cancer, anal surgery in the last 3 months, acute/painful perianal disease.
Statistical methodology and analysis:	Non-inferiority testing of MAPLe in the assessment of FI will be performed using Bland Altman method. MAPLe will be tested against HRAM and AUS. Participants will be grouped according their pathology: Fistula/chronic perianal disease, Obstetric injury <12 months, Obstetric injury >12 months, neuropathic sphincter. Correlation studies and regression analysis to identify which groups benefitted from MAPLe assessment. The clinical utilisation of MAPLe will be determined by the outcome of an expert panel. Comparative analysis of participant pre and post treatment MAPLe results will identify if targeted treatment has been achieved.

3. Background and Rationale

Burdon of Disease

Faecal incontinence (FI) is defined as the involuntary passage of gas, liquid or solid stool. The symptom is experienced by an estimated 1-10% of the population. FI is associated with a multitude of disease pathologies and prevalent in vulnerable patient groups, the elderly, learning disabilities or severe co-morbidities, and most prevalent in multiparous females. The degree of symptomatic severity is varied and can result in psychological destress and social withdrawal, severely impacting quality of life in up to 22% of suffers(1).

There is significant economic burden associated with FI. Health economic studies have identified US$4110 as an average annual cost per person, with an increased cost associated with increased symptom severity(2). Further studies estimated a US $11 billion annual expenditure and a 55% increase in personal cost of health for sufferers(3). Treatment is symptom orientated, further research would improve understanding of the symptom and direct treatment for more effective outcomes.

Anatomy and Physiology of the Pelvic Floor

FI is the result of impairment to the structure or function of the pelvic floor(4). The pelvic floor, levator ani, is a sheet of muscle supporting the weight of the abdominal cavity. It is divided into four muscle groups: pubococcygeus, ilio-coccygeus, coccyges and puborectalis, assisting the maintenance of faecal and urinary continence.

The anal canal is an opening in the levator ani to allow for passage of stool. The rectum, supported by puborectalis, opens into the anal canal. The anal canal is 4cm long and surrounded by two groups of muscles forming the anal sphincter. The involuntary muscles of the internal anal sphincter (IAS), a continuation of the circular muscle of the rectum. The voluntary muscles of the external anal sphincter (EAS), derived from levator ani. The IAS provides 80% of the resting pressure of the anal sphincter(5).

The sphincter responds to local stimulation via the recto-anal reflex arc, stimulation of the internal sphincter to relax upon distension of the rectum, as well as higher neural stimulation via the spinal cord to relax the external sphincter(6). Damage to the structure of the sphincter complex or its nervous supply reduces the anal tone and results in FI of varying degrees: gas, liquid or solid stool.

Pathogenesis and Aetiology of FI

The pathogenesis of FI is associated with the pathological process of the underlying disease and classified by clinical findings: Anal sphincter weakness, anatomical disturbances of the pelvic floor, anorectal inflammation, central nervous system disease, and bowel disturbances. The most common cause of FI in females is anal sphincter weakness following obstetric injury(7) by direct damage to the sphincter or indirect damage to the pudendal nerve.

Due to the complex and multi-factorial pathogenesis(8), FI is commonly classified by the predominant symptom: passive, urge or mixed.

Current Assessment of the Pelvic Floor

FI is initially assessed in primary care to identify and address lifestyle or medical causes. Patients with persistent symptoms are referred to specialist centres for structural and functional assessment of the pelvic floor(9). Structural assessment includes endoscopy, MRI and Anal ultrasound (AUS)(10). Function, including sensitivity and compliance, is assessed by anorectal physiology studies: anorectal manometry, balloon expansion and expulsion, and barostat investigation(11). Following clinical

review, patients are referred for the appropriate investigation. Patients with symptoms of FI undergo thorough assessment of the structure and function of the anal sphincter.

Structural assessment of the anal sphincter is performed using an anal ultrasound (AUS). The AUS probe is placed into the anal canal. The transducer at the tip of the probe emits sound waves at a frequency between 2.5-6MHz, these reflect against the surrounding tissue and received by the transducer. The volume of sound waves reflected is dependent on the density of the tissue surrounding the probe. The differing structural integrities of the IAS and EAS give distinct appearances. The IAS is seen as a hypoechoic band approximately 1-3 mm in thickness. The EAS appears as a hyperechoic band surrounding the IAS with a thickness of 4-10mm. Abnormalities seen within each band such as lucencies or opacities represent pathology(12). Due to its low risk, low cost and high sensitivity, AUS is the imaging modality of choice for assessing the anal sphincter(13).

Functional assessment of the anal canal is undertaken using anorectal manometry. The technique measures the closing pressures of the anal canal. The test is performed using a probe with between 6-12 pressure sensors along its length. The manometry system can either be solid state or water perfused(14).

The probe is placed within the anal canal and pressures within the anal canal are recorded at rest, voluntary contraction and coughing. The pressures are measured in mmHg and represents the cross-sectional pressure of the canal at each level. The individual structures attributing to the pressure are not identified and the results are representation of the pressures of the pelvic floor as a whole.

Studies have been performed to identify a range for normal results of pressures within the anal canal. The results are dependent on gender and parity. Carrington et al undertook a study of 112 asymptomatic participants using high resolution anal manometry (HRAM) and identified a mean resting pressure of 33-110mmHg in females and 33-114 mmHg in males(15). Further studies have found disparity between age groups (16). Therefore, results require close and careful interpretation by the clinician, taking into account patient symptoms.

Treatment

The NHS spends an estimated £100 million on treatment for FI and it is thought patients experience symptoms for 5 years before seeking treatment. If community management of dietary advice, simple anti-diarrhoeal medication and good toileting (17) fail patients are refereed to secondary care. Choice of treatment can vary between trusts due to resources and expertise. The treatment options for FI include: medications, biofeedback, rectal irrigation, neuromodulation and other surgical interventions. Patients are referred in a stepwise progressive pattern. This directed by their response to treatment, quantified by FI scores.

Biofeedback is the process of electronically monitoring an autonomic function to acquire voluntary control. Biofeedback treatment for FI has three elements: rectal sensitivity training to improve awareness and response to stool in the rectum, strength training of the pelvic floor using manometric or electromyographic stimulus, or co-ordination training. Biofeedback treatment protocols are varied(18), however 70-80% experience a 50% improvement of symptoms (19). More recent studies have found no significant improvement in symptoms following treatment with biofeedback(20) and biofeedback has been shown to have the same symptom improvement as dietary advice and routine pelvic floor exercises(21).

Rectal irrigation is a treatment for both constipation and FI. The treatment aim is to maintain an empty rectum(22) preventing incontinence episodes(23). Irrigation is performed using a catheter placed in the rectum through which fluid is irrigated resulting in evacuation of the rectum. The treatment has been found to improve symptoms by 44%.

Neuromodulation is a second line treatment for FI in patients with persistent symptoms of FI(24). There are two forms of treatment: sacral nerve stimulation (SNS) and percutaneous tibial nerve stimulation (PTNS). The mode of action is unclear, the treatment applies stimulation to the sacral nerves improving anal sphincter function(25). SNS is an implantable neuromodulator. Prior to implantation, patients undergo a trial period by placement of a temporary wire into the 3rd sacral foramen. If a 50% reduction in symptoms is experienced the patient is offered a permanent implantable device. Studies have shown an 83% continue to have improved symptoms at the 3 years(26). PTNS is a non-implantable form of neuromodulation. The technique was initially developed for the treatment of urinary incontinence; however following reports of improved symptoms of FI further research has been undertaken. NICE references 53% of patients have a good outcome following treatment. However, a recent randomized control trial comparing outcomes following treatment with PTNS vs sham stimulation identified no significant clinical benefit following PTNS treatment(27). Currently PTNS is not recommended for the treatment of FI.

Surgery is performed on the anal sphincter when structural defects are present, most commonly following obstetric injury. The two main surgical techniques used are sphincter repair and sphincteroplasty. Sphincter repair occurs directly after child birth, and is commonly performed by the attending obstetric doctors. Sphincteroplasty is performed by specialist pelvic floor surgeons when large deficits are found on AUS.

Following treatment repeat physiological assessment is not performed as studies have found no improvement(28). Patients who continue to be symptomatic are referred for further treatments.

Rationale

FI is a symptom requiring structural and functional assessment of the anal sphincter to direct choice of treatment. Structural assessment using AUS has been proven to be sensitive(12)(29). Functional assessment can result in a disparity between symptom profile and investigation findings(30) as well as an overlap of results between healthy and symptomatic persons(31).This was shown by Lam et al who identified no correlation between ARP and FI scores in a study of 218 patients. These findings were also reflected in a study undertaken by Zutshi et al on 53 symptomatic females(28). The role of investigatory tests is to guide treatment(30) and although these tests can establish a baseline , both HRAM and AUS are poor predictors of treatment outcome(32). This identifies a need for further study into the assessment of FI.

Novel techniques investigating other properties of the anal canal have been developed. These include assessing elasticity of the anal canal and anal acoustic reflectivity. These techniques are in their early stages and studies so far have shown limited clinical utilisation(33).

Electromyography (EMG) is a technique used to assess the innervation and response of a voluntary muscle fibre to a stimulus. Traditionally EMG is performed using a single needle electrode inserted into a muscle. Following stimulus to voluntarily contract, an action potential is generated along a somatic nerve resulting in a synapse at the neuromuscular junction (NMJ), also called innervation zone, and the release of acetylcholine (ACh). ACh acts on voltage gated channels in the sarcolemma causing depolarisation from the resting potential of -60—90 mV to + 75mV (motor unit potential) resulting in contraction of the muscle fibre. The EMG needle electrode detects the depolarization and records the amplitude (mV) and frequency (Hz). This provides information on individual motor unit potentials resulting from the innervation zone but limited information on overall muscular function. EMG of the EAS requires multiple circumferential punctures into the muscle this is both invasive and painful, limiting the investigation to research and specialist cases.

Studies performed at other centers have investigated the use of surface electrodes (sEMG) on probes(34) placed anally to identify abnormalities or abnormal variants in the innervation and propagation of stimulus within the EAS(35). The anal probes have a series of circumferential sensors that identify the origin and direction of propagation of an action potential. The origin correlates to the

location of an NMJ and innervation zone(19). This technique has been used to investigate asymmetric innervation of the anal canal, particularly important in obstetric medicine(36), but has not progressed from research into clinical utilisation.

The MAPLe device is a new medically certified device distributed by Novuqare using the principals of sEMG in the diagnosis and management of pelvic floor complaints (figure 1).

Figure 1 MAPLe device: anal probe, sEMG detector and charging station.

The probe l has 24 surface electrodes positioned in circumferential bands along its length (figure 2), it is placed in the anal canal. Each sensor detects the sEMG activity in mV for the most proximal muscle fibers (figure 3).

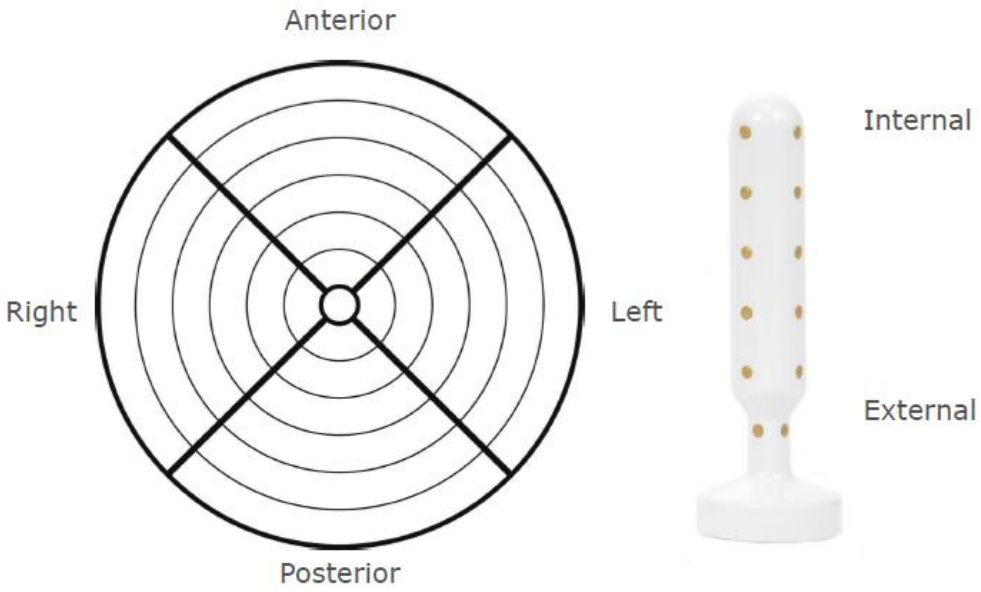


Figure 2 Each band corresponds to a circumferential group of sensors along the probe.

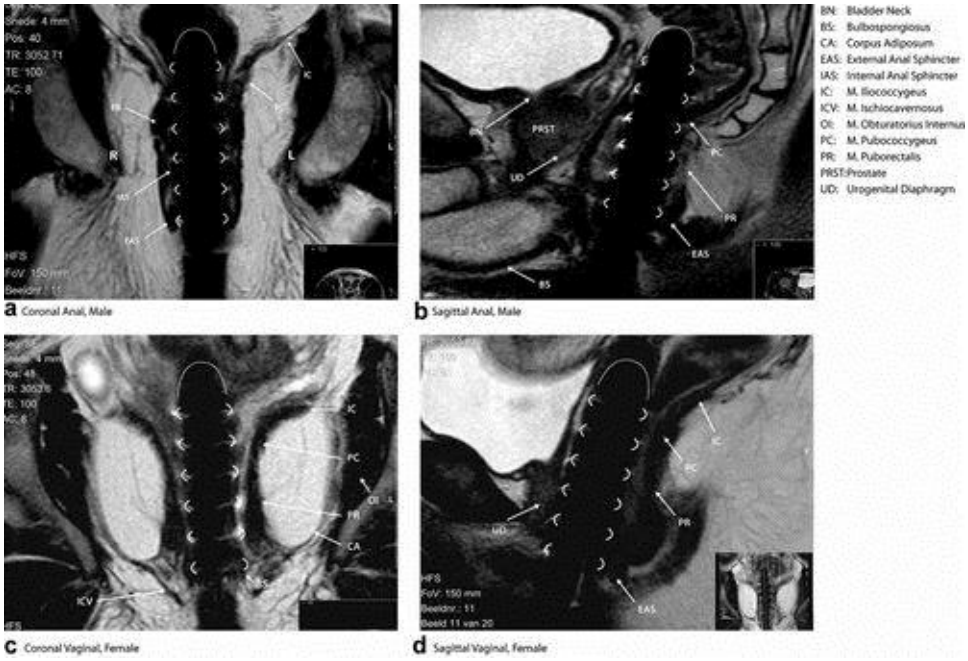


Figure 3 MRI of pelvis with anal probe in situ, confirming correct placement for sEMG detection.

The results are analysed by the receiver to provide numerical values. The values are displayed as a target shaped diagram depicting locational functionality (figure 4 & 5), giving a clear representation of precise areas of weakness in the pelvic floor.

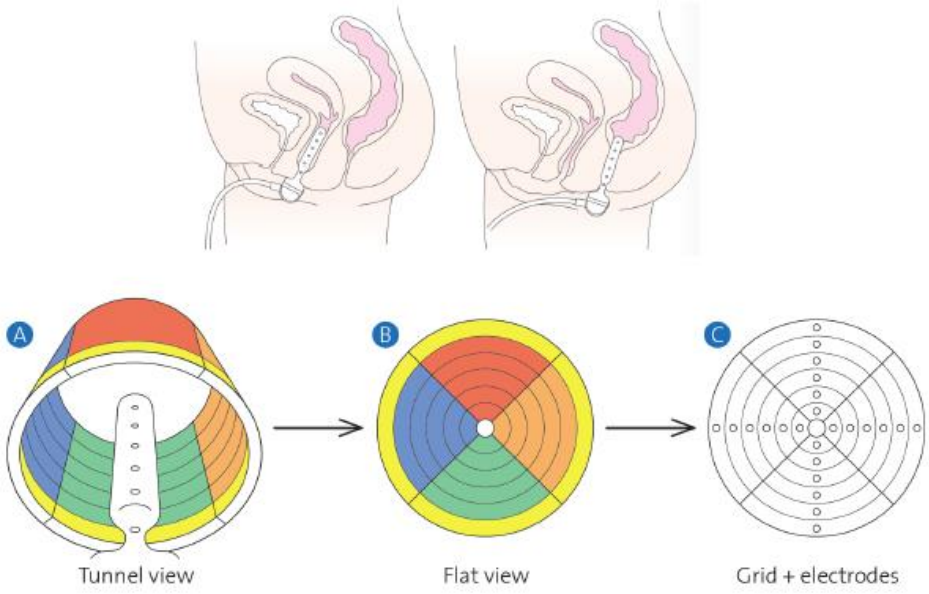


Figure 4 The results can be displayed in three views.

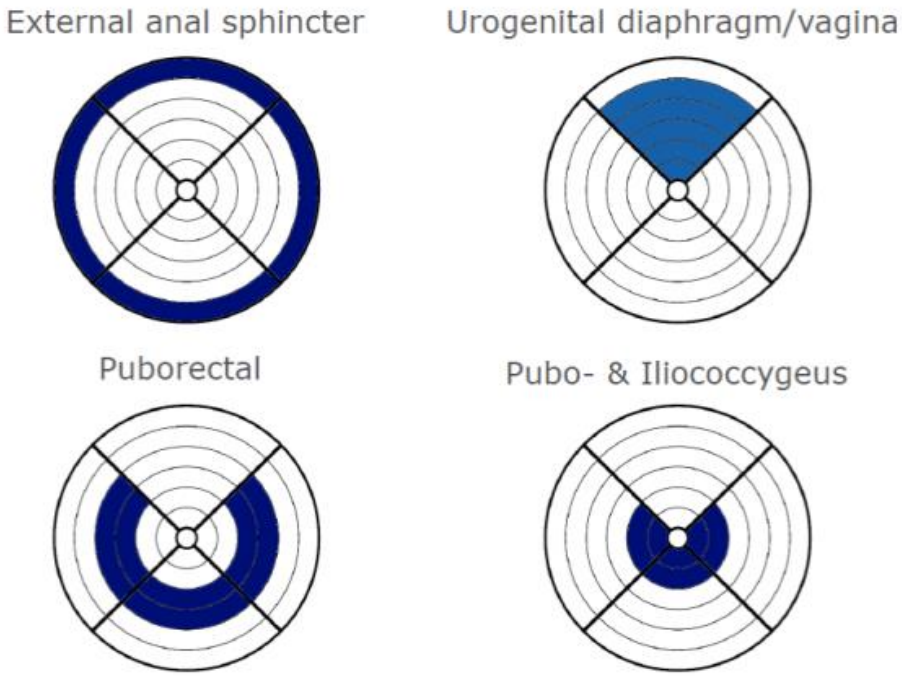


Figure 5 Sensors are grouped together according to the muscle they represent.

The results are displayed on a hand held device in both numerical and diagrammatic formats (figure 6).

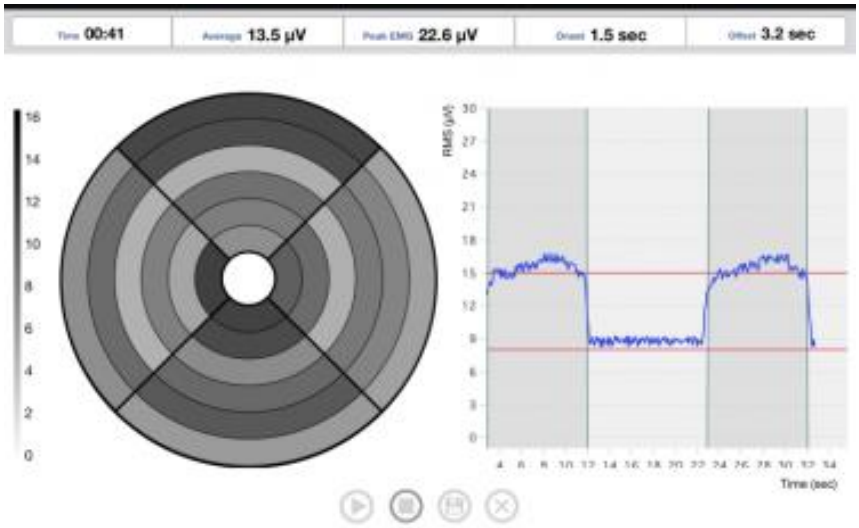


Figure 6 Results are displayed on screen in greyscale on target or numerical value.

An independent study tested MAPLe on 229 asymptomatic healthy participants. The study confirmed accurate probe placement to ensure sEMG correlated with correct muscular group, and identified a normal range (27). MAPLe is currently used to provide biofeedback for patients with FI by identifying and targeting muscles with reduced sEMG via visual and electrical stimulation.

The role of sEMG in clinical assessment of FI has been limited to research and has not been correlated with current gold standard techniques. This study aims to investigate the sEMG of symptomatic patients using MAPLe. The study will test the non-inferiority of MAPLe against HRAM and AUS in assessing FI. Non-inferiority of a test is defined as the test being no worse than the competitor. The study will aim to identify if particular patient groups have closer correlation

between symptom profiles and FI scores and sEMG results, and whether sEMG improves following treatment. The study will endeavor to identify the clinical utilisation of sEMG in FI.

3.1 Assessment and Management of Risk

The table below summarise the risks and mitigations of all test above standard care that are being performed in a table:

Intervention	Potential risk	Risk Management
Assessment with MAPLe device	The device will be placed anally and record sEMG, not providing stimulation. As the device will be used in the same nature as current assessment devices no additional risk is perceived.	Performed by trained operator.

4. Objectives

Primary: To determine the role of MAPLe in the assessment of FI in defined patient groups.

Secondary: To determine if targeted treatment is achieved following assessment with MAPLe.

5. Trial design

This is cohort study of participants with symptoms of faecal incontinence. It will take place across two hospital trusts, both able to provide specialist pelvic floor services and facilities required to meet the needs of the study and follow up required by the participants. The use of two sites aims to increase the yield and diversity of participants. The sample size for the study is 120 participants.

Following a stringent selection and recruitment process, participants will be invited to a designated ARP session where they will be consented, complete an incontinence and quality of life questionnaire, and undergo ARP assessment. This will comprise of the current gold standard, AUS and HRAM, and additional assessment with MAPLe using a standardised protocol. Through undertaking all three tests participants will act at their own controls. Participant participation will conclude following ARP assessment unless treatment is deemed necessary by their local MDT. These participants will be followed up at 6 months with interval MAPLe assessment and incontinence and quality of life questionnaire.

The results will undergo statistical analysis to determine non-inferiority of MAPLe in assessing FI. For analysis participants will be allocated to the following groups: fistula/chronic perianal conditions, obstetric injury <12 months, obstetric injury >12months, neurogenic. Each group will be analysed using symptoms profile and MAPLe results to identify correlation. Comparison of MAPle results pre and post treatment will determine if targeted treatment has been achieved.

An expert panel of pelvic floor specialists will be formed to determine the additional benefit of MAPLe in a clinical context. The panel will consist of 3-6 specialists within the field. To reduce bias,

each specialist will be provided with literature on the background of MAPLe and how to analyse the results. The panelists will receive up to date guideline on the management of FI. The panel will be provided with cases and ARP results to answer the following questions:

Question 1: What is the additional benefit of MAPLe?

- Panelists will be provided with clinical history HRAM and AUS results
  - What is the diagnosis and how will you manage this patient?
- MAPLe results provided
  - Has the management changed?
  - How beneficial on scale 1-10 has the addition been?

Question 2: HRAM and AUS vs MAPLe and AUS

- Panelists will be provided with a series of paired histories set one with HRAM and AUS results, set two with MAPLe and AUS results
  - What is the diagnosis and treatment?
  - How confident do you feel in your diagnosis and treatment for set two?

Question 3: MAPLe alone

- Panelists will be provided with history and MAPLe results
- What is the diagnosis and treatment?
- Do you feel enough information is provided by the MAPLe to allow for a management plan?

The outcomes of the expert panel will undergo statistical analysis.

6. Selection of Participants

6.1 Inclusion Criteria

1. Over and including 18 years
2. Male and female
3. Symptoms of faecal incontinence
4. Willing and able to provide written informed consent.

6.2 Exclusion Criteria

1. Painful or acute perianal conditions: fissures/perianal abscess/recent trauma
2. Anal cancer
3. Anorectal surgery in the last 3 months

6.3 Recruitment

Referrals to each trust are triaged by the overseeing consultant. Potential participants for the study will be identified. At ASPH suitable referrals will be tracked to a dedicated pelvic floor clinic for review by the student researcher. Participants who meet the inclusion/exclusion criteria will be offered a patient information sheet and given an appointment in a dedicated anorectal physiology session (ARP). At UCLH suitable referrals will be contacted via telephone by the student researcher, should they wish to enroll they will receive a PIS and given an appointment in a dedicated ARP session. Participants will only be assessed and followed up in their recruiting trust.

Participant recruitment at a site will only commence when the trial has:

1. Been confirmed by the Sponsor (or it's delegated representative), and
2. Been issued an 'NHS permission letter'.

6.4 Informed consent

It is the responsibility of the Investigator, or a person delegated by the Investigator to obtain written informed consent from each participant prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the trial.

The student researcher is suitably qualified and experienced in the consent process, and has been delegated this duty by the CI/ PI on the Staff Signature and Delegation of Tasks.

"Adequate time" must be given for consideration by the participant before taking part. Consent will be sought at least 24 hours after being given the study documentation It must be recorded in the medical notes when the participant information sheet (PIS) has been given to the participant.

The Investigator or designee will explain that participants are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.

No trial procedures will be conducted prior to the participant giving consent by signing the Consent form. Consent will not denote enrolment into trial.

A copy of the signed Informed Consent form will be given to the participant. The original signed form will be retained in the trial file at site and a copy placed in the medical notes.
The PIS and consent form will be reviewed and updated if necessary throughout the trial (e.g. where new safety information becomes available) and participants will be re-consented as appropriate.

7. Product/Interventions

The study is investigating the use of the MAPLe device in the assessment of FI. The MAPLe is a medically certified device distributed by Novuqare (Appendix 2). The certification covers the diagnosis and management of faecal and urinary incontinence; it will be used within in its certification.

The MAPLe device consists of a probe that can be used vaginally or anally and an electric receiving device. The probe has 24 surface electrodes that detect the electromyography (EMG) of the different groups of muscles of the pelvic floor. These results are analysed by the receiver to provide numerical values and greyscale depiction of the EMG of each muscle group and location of reduced or increased activity.

For the assessment of faecal incontinence the probe will be placed anally. The participant will be asked to perform a set protocol of maneuvers to identify areas of weakness in the pelvic floor. Participants will undergo assessment with MAPLe at the ARP session.

8. Study procedures

8.1 Pre-intervention assessments

The following study specific procedures will be carried out after consent to assess the participant's eligibility:

- Medical History recorded
- Surgical History recorded
- Concomitant Medication recorded

All pre-treatment procedures will be carried out as specified in the schedule of assessments (appendix 1).

8.2 Registration Procedures

Participant registration will be undertaken centrally by the **student researcher** when booking ARP. Eligibility will be confirmed and participants will be allocated an individual study number. At ARP participants will complete a pre-filed consent form.

Participants are considered to be enrolled into the study following: consent, pre-treatment assessments (see section 8.1), confirmation of eligibility, completion of the registration process, allocation of the participant study number by the central coordinating team.

8.3 Intervention procedures

Participants will be asked to attend an ARP session at their recruiting trust **to undertake assessment by the student researcher**. During this session each participant will complete an incontinence questionnaire (appendix 3), quality of life questionnaire(37) (appendix 4), provide a prescribed history (appendix 5) and undergo standardised ARP studies (appendix 6, 7):

Anal ultrasound

- UCLH: performed in the radiology department by trained sonographer.
- ASPH: performed during anorectal physiology session by trained study representative

HRAM

- Performed at anorectal physiology session by trained study representative

MAPLe

- Performed at anorectal physiology session by trained study representative.

8.4 Subsequent assessments and procedures

The ARP results for each participant will be discussed at their local multi disciplinary team meeting in accordance with current practice. Participants who are offered treatment will be followed up at 6 months in their recruiting trust for repeat assessment with MAPLe. Participants who are offered neuromodulation will receive interval assessment with MAPLe during the placement of the implanted device. Should not follow up be offered participation is complete.

A schedule of all trial assessments and procedures is set-out in Appendix 1.

8.5 Discontinuation/withdrawal of participants

In consenting to participate in the study, participants are consenting to intervention, assessments, follow-up and data collection.

A participant may be withdrawn from trial whenever continued participation is no longer in the participant's best interests, but the medical reasons for doing so will be recorded. Personal reasons will not be recorded. Reasons for discontinuing the trial may include:

- Ineligibility undetected at screening
- Deviation from protocol
- Significant non-compliance with study requirements (refusal/difficult examination)
- Withdrawal of consent

The participants will remain in the study for the purpose of data analysis and the reason for withdrawal recorded in the CRF and medical notes. If a participant explicitly states they do not wish to contribute further data to the trial their decision must be respected and recorded in the CRF and medical notes.

8.6 Definition of End of Study

The expected duration of the study is 18 months from recruitment of the first participant.
The end of study is 6 months following the date of the last visit of the last participant.

9. Recording and reporting of adverse events

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or trial participant, which does not necessarily have a causal relationship with the intervention involved.
Serious Adverse Event (SAE).	Any adverse event that: - results in death - is life-threatening* - requires hospitalisation or prolongation of existing hospitalisation** - results in persistent or significant disability or incapacity, or - consists of a congenital anomaly or birth defect.
* A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE.	

9.2 Assessments of Adverse Events

Each adverse event will be assessed for severity, causality, seriousness and expectedness as described below.

9.2.1 Severity

Category	Definition
Mild	The adverse event does not interfere with the participant's daily routine, and does not require further intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the participant's routine, or requires further intervention, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

9.2.2 Causality

The assessment of relationship of adverse events to the intervention is a clinical decision based on all available information at the time of the completion of the case report form.

The following categories will be used to define the causality of the adverse event:

Category	Definition
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatments).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

9.2.3 Expectedness

There are no expected adverse events.

9.3 Recording adverse events

All Adverse events will be recorded in the CRF following consent.

9.4 Procedures for recording and reporting Serious Adverse Events

All serious adverse events will be recorded in the medical records and the CRF, and the sponsor's AE log. The AE log of SAEs will be reported to the sponsor at least once per year.

All SAEs must be recorded on a serious adverse event (SAE) form. The PI or designated will complete the sponsor's SAE form and the form will be emailed to the Sponsor within 5 working days of becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

Where the event is unexpected and thought to be related to the intervention, this must be reported by the Investigator to the Health Research Authority within 15 days.

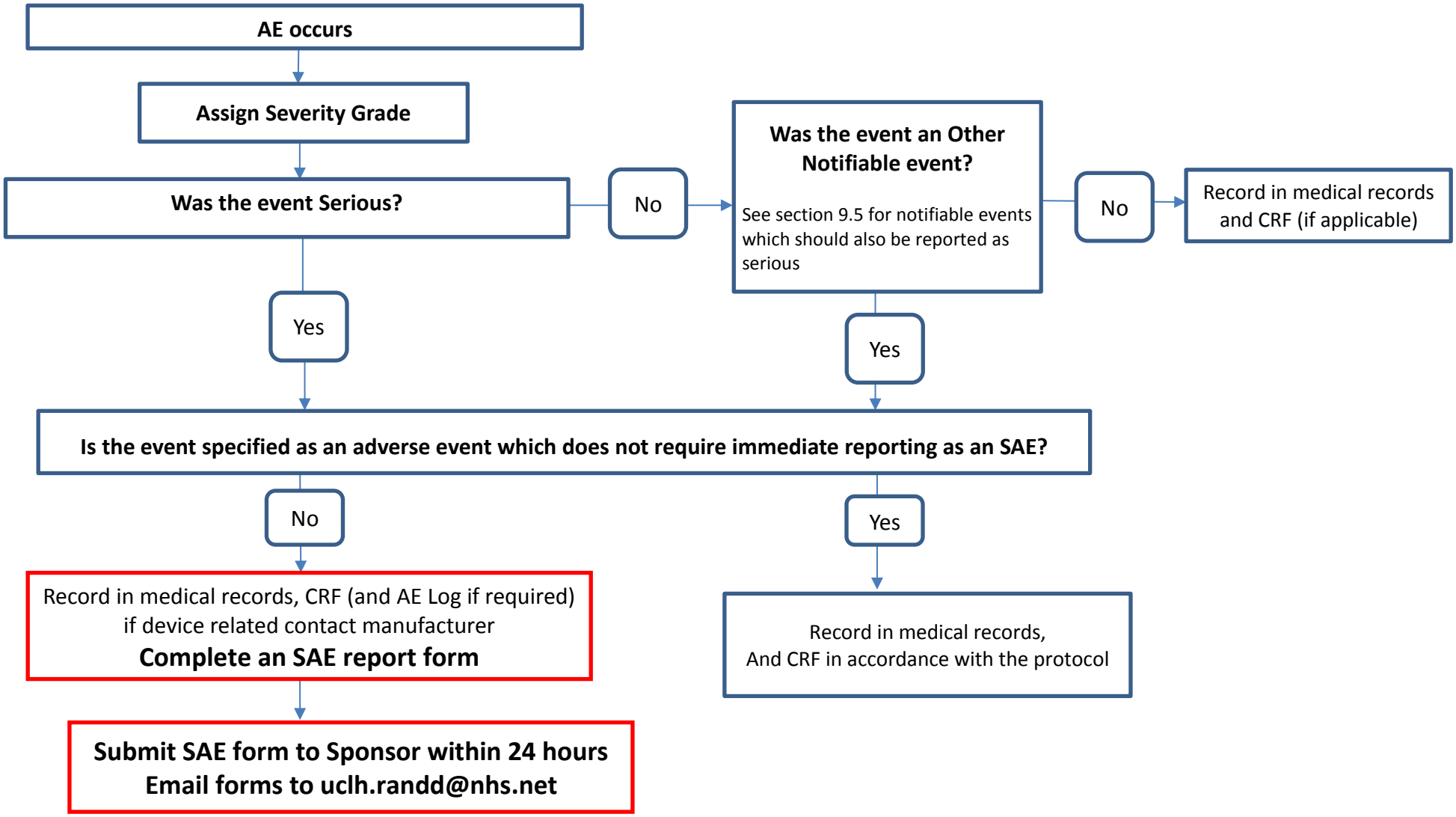
Completed SAE forms must be sent within 5 working days of becoming aware of the event to the Sponsor

Email forms to Research-incidents@ucl.ac.uk

SAEs will be reported to the sponsor until the end of the trial.

Participants must be followed up until clinical recovery is complete. Follow-up SAE forms (clearly marked as follow-up) should be completed and emailed to the JRO as further information becomes available.

Flow Chart for SAE reporting



9.5 Reporting Urgent Safety Measures

If any urgent safety measures are taken the CI/ PI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC and Sponsor of the measures taken and the circumstances giving rise to those measures.

9.6 Notification of reportable protocol violations

A reportable protocol violation is a breach which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the participants of the study; or
- the scientific value of the study.

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

9.7 Reporting incidents involving a medical device

All adverse event reporting will be undertaken by a study representative. If the event is in relation to MAPLe the event will be reported to the manufacturer Medtronic via the Sales support worker Rosemary Ledger.

Adverse events involving routine devices, AUS and HRAM, will be reported locally within each trust in accordance with local trust guidelines.

All incidents will be reported as soon as possible (usually within 24 hours).

9.8 Trust Incidents and Near Misses

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a) It is an accident or other incident which results in injury or ill health.

b) It is contrary to specified or expected standard of patient care or service.

c) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.

d) It puts the Trust in an adverse position with potential loss of reputation.

e) It puts Trust property or assets in an adverse position or at risk.

Incidents and near misses must be reported to the Trust through DATIX as soon as the individual becomes aware of them.

A reportable incident is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a) It is an accident or other incident which results in injury or ill health.

b) It is contrary to specified or expected standard of patient care or service.

c) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.

d) It puts the Trust in an adverse position with potential loss of reputation.

e) It puts Trust property or assets in an adverse position or at risk of loss or damage.

10. Data management

10.1 Confidentiality

All data will be handled in accordance with the UK Data Protection Act 2018.

The Case Report Forms (CRFs) will not bear the participant's name or other personal identifiable data. The study identification number will be used for identification and this will be clearly explained to the patient in the PIS. Patient consent for this will be sought.

10.2 Data collection tools and source document identification

Data will be collected from sites on study specific case report forms (CRFs) or data collection tools such as electronic CRFs.

Source data are contained in source documents and must be accurately transcribed on to the CRF. All data will be recorded in the local notes and CRF.

All data required for the study will be obtained during the anorectal physiology session, minimising the risk of incomplete data sets.

10.3 Completing Case Report Forms

All CRFs must be completed and signed by staff that are listed on the site staff delegation log and authorised by the CI/ PI to perform this duty. The CI/PI is responsible for the accuracy of all data reported in the CRF.

Once completed CRFs will remain within each parent trust and stored in a designated locked filing cabinet. They will not be removed from their trust site.

10.4 Data handling

The study is compliant with the requirements of General Data Protection Regulation (2016/679) and the Data Protection Act (2018). All investigators and study site staff will comply with the requirements of the General Data Protection Regulation (2016/679) with regards to the collection, storage, processing and disclosure of personal information, and will uphold the Act's core principles. UCL is the data controller; the UCL Data Protection Officer is Lee Shailer data-protection@ucl.ac.uk. The data processors are the Student Researcher and the Chief Investigator. The study will be collecting the following data: Age, gender, parity, medical and surgical history, drug history.

Once a participant is enrolled, they will be allocated an individual study number. No record of name/date of birth/address/telephone number will be made. A list of individual study number and associated hospital numbers will be recorded in an encrypted database on a computer within each trust. The list will only comprise of participants recruited from that trust. Data will be provided directly by the participants and recorded on a CRF by the student investigator. Investigation results will be recorded on the CRF. The CRF will not record personal data. The CRF and completed questionnaires will be stored in a locked filing cabinet in the GI physiology department at each trust only accessible to study personnel. The anonymised research data will be collated by the student researcher in an encrypted database on each trust computer. For analysis, a copy of the research data obtained at ASPH will be made and placed on an encrypted USB. This will be transferred to UCLH and combined with the research data from this site. This will be undertaken by the student researcher. The CRF and associated documents will be destroyed 2 years following completion of study by their trust. The electronic database will be stored for 5 years.

11. Statistical Considerations

11.1 Primary Outcome

They primary outcome is to determine which participant groups benefit from assessment with MAPLe. Benefit will be determined by correct identification of abnormalities in symptomatic participants using MAPLe, correlation between symptom profile and MAPLe results, and the outcome of the expert panel. It will be measured once the end of recruitment is reached.

11.2 Secondary outcome(s)

The secondary outcome is to determine if following assessment with MAPLe targeted treatment is achieved. This will be defined by improvement in physiological assessment with MAPLe and incontinence questionnaires. This will be measured at 6 months following the end of recruitment at the end of study.

11.3 Sample size calculation

The sample size has not been formally calculated at this time. This is due to no previous studies on this area being performed. A pilot study to identify the 'normal' measurements for the MAPLe stipulated 30 participants per group to identify a statistically significant result. Accounting for 4 participant groups a sample size of 120 has been set.

11.4 Planned recruitment rate

Participants will be recruited throughout the duration of the study. An anticipated recruitment rate is 2-3 participants per week over 12 months to meet the sample size.

11.5 Statistical analysis

11.5.1 Primary outcome analysis

Non-inferiority testing of MAPLe will be performed using Bland-Altman method. Correlation between MAPLe and AUS for location of sphincter abnormality will be identified. Correlation between MAPLe and HRAM for functional abnormalities will be identified.

Participants will be allocated a patient group dependent on the cause of FI:

- Fistula/ chronic perianal conditions
- Obstetric injury <12 months
- Obstetric injury > 12 months
- Neuropathic

Each group will be analysed using correlation studies and regression analysis to determine which groups benefit from MAPLe assessment.

The clinical benefit of the addition of MAPLe assessment will be determined from the analysis of the results of the expert panel.

11.5.2 Secondary outcome analysis

To determine if targeted treatment has been achieved participants will be grouped according to the treatment received: biofeedback, neuromodulation, rectal irrigation, and surgery.

Statistical comparison between MAPLe results pre and post treatment for each participant per group will be performed and analysed.

12. Record keeping and archiving

At the end of the trial, all essential documentation will be archived securely by the CI for a minimum of 20 years from the declaration of end of trial.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with all applicable regulatory requirements.

The sponsor will notify sites when trial documentation can be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

13. Oversight Committees

13.1 Trial Management Group (TMG)

The TMG will include the Chief Investigator and trial staff. The TMG will be responsible for overseeing the trial. The group will meet regularly, once per week at each site and will send updates to PIs.

The TMG will review recruitment figures, SAEs and substantial amendments to the protocol prior to submission to the REC. All PIs will be kept informed of substantial amendments through their nominated responsible individual.

13.2 Other committees

The role of the TSC is to provide overall supervision of the trial. The TSC will review the data, adverse events and any other issues identified and recommend any appropriate amendments/actions for the study as necessary. The TSC acts on behalf of the funder and Sponsor.

14. Ethical requirements and patient and public involvement

Ethics

The sponsor will ensure that the trial protocol, participant information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate research ethics committee, prior to any participant recruitment. The protocol, all other supporting documents including and agreed amendments, will be documented and submitted for ethical and regulatory approval as required. Amendments will not be implemented prior to receipt of the required approval(s).

Before any NHS site may be opened to recruit participants, the Chief Investigator/Principal Investigator or designee must receive confirmation of capacity and capability in writing from the Trust Research & Development (R&D). It is the responsibility of the CI/ PI or designee at each site to ensure that all subsequent amendments gain the necessary approvals, including confirmation of capacity and capability at the site. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual participants (see section 9.6 for reporting urgent safety measures).

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favorable opinion was given, and annually until the trial is declared ended. The chief investigator will prepare the APR.

Within 90 days after the end of the trial, the CI/Sponsor will ensure that the main REC is notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the Sponsor with a summary report of the trial, which will then be submitted to the REC within 1 year after the end of the trial.

Patient and public involvement (PPI)

The study recognises the importance of patient involvement in. A patient survey in outpatient clinic was performed. The survey asked the following questions:

- How does FI Impact your life?
- Do you therein there is a role for further investigating FI?
- Would additional testing at a routine appointment be an acceptable method for the study?
- If a study was recruiting would you participate?

The patient response was positive, with all those surveyed expressing need for investigation and willingness to participate. The method was also identified as acceptable.

15. Monitoring

The sponsor has determined the study to be low risk and has advised the following monitoring process:

Each site to e-mail the sponsor annually:

- Delegation log
- Adverse event log
- Deviation log
- Minutes of Trial Steering Committee
- Annual progress report (Lead site only) when sent to Ethics Committee

16. Finance

The study has been funded by the GI Physiology Unit at UCLH. 2 MAPLe devices have been purchased by the departmental charity. Ongoing funding has been agreed by each trust for the purchasing of probes to be used within each trust. There are no financial interests in they study.

17. Insurance

University College London holds insurance against claims from participants for injury caused by their participation in the trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the trial. University College London does not accept liability

for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this trial shall provide negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

The MAPLe is covered by a 3 year indemnity. Should the device break or malfunction it will be returned to the manufacturer for repairs and a replacement provided. Should the original device be irreparable it will be replaced free of charge.

18. Intellectual property

All background intellectual property rights (including licenses) and know-how used in connection with the study shall remain the property of the party introducing the same and the exercise of such rights for purposes of the study shall not infringe any third party's rights.

All intellectual property rights and know-how in the protocol and in the results arising directly from the study, but excluding all improvements thereto or clinical procedures developed or used by each participating site, shall belong to UCLH. Each participating site agrees that by giving approval to conduct the study at its respective site, it is also agreeing to effectively assign all such intellectual property rights ("IPR") to UCL and to disclose all such know-how to UCL.

Each participating site agrees to, at the request and expense of UCL execute all such documents and do all acts necessary to fully vest the IPR in UCL.

Nothing in this section shall be construed so as to prevent or hinder the participating site from using know-how gained during the performance of the study in the furtherance of its normal activities of providing or commissioning clinical services, teaching and research to the extent that such use does not result in the disclosure or misuse of confidential information or the infringement of an intellectual property right of UCL. This does not permit the disclosure of any of the results of the study, all of which remain confidential.

19 Appendices

Appendix 1 - Schedule of assessments

	Screening (Pre-treatment assessment)	**Intervention phase**		**Final visit**
Visit No:	1	2	3	4
	Day – X to Day -X	Day 1	Day 7	6 Months
Window of flexibility for timing of visits:			+/- 7 Days	+/- 14 days
Informed Consent		X		
Medical History	X			
Physical Examination				
Eligibility confirmation	X	X		
Faecal incontinence Questionnaire		X		
Quality of Life Questionnaire	X			
Anal Ultrasound	UCLH X	ASPH X		
Prescribed History		X		
HRAM		X		
MAPLe		X		If treatment advised x
MDT			X	
Adverse Events review	X	X	X	X
Concomitant Medication review (if applicable)	X	X		

Appendix 2 - CE Certificate

Please see attached PDF

Appendix 3 - St Mark's Incontinence Score

St Mark's Incontinence Score

	Never	Rarely	Sometimes	Weekly	Daily
Incontinence for solid stool	0	1	2	3	4
Incontinence for liquid stool	0	1	2	3	4
Incontinence for gas	0	1	2	3	4
Alteration in lifestyle	0	1	2	3	4

	Yes	No
Need to wear pad or plug	0	2
Taking constipating medications	0	2
Lack of ability to defer defacation for 15 mins	0	4

Definitions

Never: No episodes in the past 4 weeks

Rarely: One episode in the past 4 weeks

Sometimes: More than one episode in the past 4 weeks but less than once per week

Weekly: One or more episodes per week but less than one per day

Daily: One or more episodes per day

Appendix 4 - Quality of Life Questionnaire

Quality of life Questionnaire

Q 1: In general, would you say your health is:
1 [] Excellent
2 [] Very Good
3 [] Good
4 [] Fair
5 [] Poor

Q2: For each of the items, please indicate how much of the time the issue is a concern for you due to accidental bowel leakage. (If it is a concern for you for reasons other than accidental bowel leakage then check the box under Not Apply, (N/A).)

Due to accidental bowel leakage	Most of the Time	Some of the Time	A little of the time	None of the Time	N/A
I am afraid to go out	1	2	3	4	
I avoid visiting friends	1	2	3	4	
I avoid staying overnight away from home	1	2	3	4	
It is difficult for me to get out and do things like going to a movie or to church	1	2	3	4	
I cut down on how much I eat before I go out	1	2	3	4	
Whenever I am away from home, I try to stay near a restroom as much as possible	1	2	3	4	
near a restroom as much as possible	1	2	3	4	
It is important to plan my schedule around my bowel pattern	1	2	3	4	
I avoid traveling	1	2	3	4	
I worry about not being able to get to the toilet in time	1	2	3	4	
I feel I have no control over my bowels	1	2	3	4	
I can't hold my bowel movement long enough to get to the bathroom	1	2	3	4	
I leak stool without even knowing it	1	2	3	4	
I try to prevent bowel accidents by staying very near a bathroom	1	2	3	4	

Q3: Due to accidental bowel leakage, indicate the extent to which you AGREE or DISAGREE with each of the following items. (If it is a concern for you for reasons other than accidental bowel leakage then check the box under Not Apply, N/A).

Due to accidental bowel leakage:	Strongly Agree	Somewhat Agreee	Somewhat Disagree	Strongly Disagree	N/A
I feel ashamed	1	2	3	4	
I an not do many of things I want to do	1	2	3	4	
I worry about bowel accidents	1	2	3	4	
I feel depressed	1	2	3	4	
worry about others smelling stool on me	1	2	3	4	
I feel like I am not a healthy person	1	2	3	4	
I enjoy life less	1	2	3	4	
I have sex less often than I would like to	1	2	3	4	
I feel different from other people	1	2	3	4	
The possibility of bowel accidents is always on my mind	1	2	3	4	
I am afraid to have sex	1	2	3	4	
I avoid traveling by plane or train	1	2	3	4	
I avoid going out to eat	1	2	3	4	
Whenever I go someplace new, I specifically local where the bathrooms are.	1	2	3	4	

Q 4: During the past month, have you felt so sad, discouraged, hopeless, or had so many problems that you wondered if anything was worthwhile?

1 [] Extremely So - To the point that I have just about given up
2 [] Very Much So
3 [] Quite a Bit
4 [] Some - Enough to bother me
5 [] A Little Bit
6 [] Not At All

Scales range from 1 to 5, with a 1 indicating a lower functional status of quality of life. Scale scores are the average (mean) response to all items in the scale (e.g., add the responses to all questions in a scale together and then divide by the number of items in the scale. Not Apply is coded as a missing value in the analysis for all questions.)
Scale 1. Lifestyle, ten items: Q2a Q2b Q2c Q2d Q2e Q2g Q2h Q3b Q31 Q3m
Scale 2. Coping/Behaviour, nine items: Q2f Q2i Q2j Q2k Q2m Q3d Q3h Q3j Q3n
Scale 3. Depression/Self Perception, seven items: Q1 Q3d Q3f Q3g Q3i Q3k Q4, (Question 1 is reverse coded.)
Scale 4. Embarrassment, three items: Q21 Q3a Q3e

Appendix 4 – London protocol for performing HRAM

(1) **Stabilisation** – a minimum of 3 minutes stabilisation period should be allowed. The patient should be asked to lie still, relaxed, without talking if possible. During this time it is useful to mark the limits of the anal canal for future reference;

(2) **Resting period** – a 1-minute period of measurement at rest should be taken, again with the patient relaxed and without talking. Any sudden movement (e.g. talking, coughing etc.) should be noted on the trace to prevent confusion during *post hoc* analysis;

(3) **Squeeze manoeuvre** – three squeezes, each of 5 seconds duration and separated by 30 second rest periods, should be performed in response to the (suggested) following command "please squeeze in tight with the muscles around your bottom and hold until I say stop". A 30 second rest period should also be allowed following the third manoeuvre;

(4) **Endurance squeeze manoeuvre** – a single 30 second endurance squeeze should be performed in response to the (suggested) following command "please squeeze in tight with the muscles around your bottom. This time I would like you to hold on for 30 seconds, or as long as you can". The patient should be encouraged to continue squeezing during the 30 second period to aid compliance. A 60 second rest period should be allowed following this manoeuvre;

(5) **'Push' manoeuvre** – three 15 second pushes (simulated defaecation), each separated by a 30 second rest period, should be performed in response to the (suggested) following command "please push / bear down as if you were going to the toilet to open your bowels". A 30 second rest period should be allowed following the third manoeuvre;

(6) **Cough manoeuvre** – two *single* coughs, separated by a 30 second rest period, should be performed, with the patient encouraged to cough as forcefully as possible. The patient should be instructed to refrain from coughing multiple times, as this impairs data interpretation. A 30 second rest period should be allowed following the second manoeuvre;

(7) **Rectoanal inhibitory reflex (RAIR)** – if this test is to be performed, the balloon should be inflated (ideally with an automated pump) at a rate of 30 ml/second to a volume of 60 ml. If the reflex is absent, increase the inflation volume in 60 ml increments (to a maximum of 240 ml) until the reflex is observed and sustained;

(8) **Rectal sensory testing** – rectal sensory testing should ideally be performed with an automated pump attached to the anorectal catheter. Using a ramp (continuous) inflation paradigm, the balloon should be inflated at a rate of 2 ml/second and the patient asked to report: (1) volume for first constant sensation, (2) desire to defaecate volume, and (3) maximum tolerated volume;

(9) **Rest period** – a final 30 second post-procedure period of rest should be recorded.

Appendix 5 - Protocol for MAPLe

(1) **Stabilisation** – a minimum of 3 minutes stabilisation period should be allowed. The patient should be asked to lie still, relaxed, without talking if possible. During this time it is useful to mark the limits of the anal canal for future reference;

(2) **Squeeze manoeuvre** – three squeezes, each of 5 seconds duration and separated by 30 second rest periods, should be performed in response to the (suggested) following command "please squeeze in tight with the muscles around your bottom and hold until I say stop". A 30 second rest period should also be allowed following the third manoeuvre;

(3) **Endurance squeeze manoeuvre** – a single 30 second endurance squeeze should be performed in response to the (suggested) following command "please squeeze in tight with the muscles around your bottom. This time I would like you to hold on for 30 seconds, or as long as you can". The patient should be encouraged to continue squeezing during the 30 second period to aid compliance. A 60 second rest period should be allowed following this manoeuvre;

(4) **'Push' manoeuvre** – three 15 second pushes (simulated defaecation), each separated by a 30 second rest period, should be performed in response to the (suggested) following command "please push / bear down as if you were going to the toilet to open your bowels". A 30 second rest period should be allowed following the third manoeuvre;

(5) **Cough manoeuvre** – two *single* coughs, separated by a 30 second rest period, should be performed, with the patient encouraged to cough as forcefully as possible. The patient should be instructed to refrain from coughing multiple times, as this impairs data interpretation. A 30 second rest period should be allowed following the second manoeuvre;

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