JRMO Research Protocol for Interventional Studies

Full Title	*Percutaneous infracoccygeal Botulinum toxin injection to puborectalis for the treatment of dyssynergic defaecation: a prospective observational study*
Short Title	Infracoccygeal Botox for Dyssynergia
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List of central facilities	National Bowel Research Centre, Barts and the London School of Medicine and Dentistry, Professor Charles Knowles 4 Newark Street, London, E1 2AT.

1. Contents

2. Glossary

AE	Adverse Event
AR	Adverse Reaction
BHT	Barts Health NHS Trust
BSFS	Bristol Stool Form Scale
BTXA	Botulinum Toxin type A
CI	Chief investigator
CCCS	Cleveland Clinic constipation score
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
DD	Dyssynergic defaecation
EMG	Electromyography
FI	Faecal Incontinence
GP	General Practitioner
IBS	Irritable bowel syndrome
IBS-C	Irritable bowel syndrome with predominant constipation
ICF	Informed Consent Form
MDT	Multidisciplinary Team
NBRC	National Bowel Research Centre
NICE	The National Institute for Clinical Excellence
PI	Principal Investigator
PIS	Participant Information Sheet
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SMG	Study Management Group
SMIS	St. Mark's incontinence score
USS	Ultrasound scan

3. Signature page

CI Agreement

The study, as detailed within this Research Protocol, will be conducted in accordance with the principles of Good Clinical Practice (GCP), the UK Policy Framework for Health and Social Care Research, and the Declaration of Helsinki and any other applicable regulations. I agree to take responsibility for the statistical analysis and oversight of this study.

CI Name: **Prof CH Knowles**_____

Signature: _____ 

Date: **03.10.19**_____

4. Summary and synopsis

Short title	*Infracoccygeal Botox for Dyssynergia*
Methodology	*Prospective observational study*
Research Site	*Royal London Hospital – Barts Health NHS Trust*
Objectives / aims	*Primary objective:* - *To demonstrate technical feasibility of percutaneous infracoccygeal Botulinum toxin type A (BTXA) injection as an alternative to transanal injection to puborectalis muscle for the treatment of dyssynergic defaecation.* *Secondary objectives:* - *To assess safety of this technique* - *To assess patient acceptability of this technique* - *To derive pilot clinical efficacy data to inform future trials*
Number of participants	*10*
Inclusion and exclusion criteria	*Inclusion criteria:* - *Adult patients (age 18 - 80)* - *Diagnosis of dyssynergic defaecation by published criteria* - *Ability to understand written and spoken English* - *Ability and willingness to give informed consent* *Exclusion criteria:* - *Paediatric patients (age under 18)* - *Contraindications to BTXA, including pregnancy* - *Contraindications to infracoccygeal injection* - *Morbid obesity (BMI ≥ 40)*
Statistical methodology and analysis (if applicable)	*Not applicable (descriptive summary statistics only)*
Study duration	*12 months*

5. Introduction

5.1 Background

Patients with dyssynergic defaecation represent a subgroup of a larger group of patients presenting with symptoms of chronic constipation. The disorder is characterised by impaired stool expulsion as a result of inappropriate contraction of the pelvic floor musculation despite normal propulsive force during attempted defaecation.[1] Failure of the puborectalis and/or anal sphincter muscles to relax during evacuation leads to a closed anal canal which prevents the emptying of stools. [1, 2]

A Cochrane review in 2014[2] on the treatment of chronic constipation in adults demonstrated a high prevalence of dyssynergic defaecation and a variety of treatments. In this group, biofeedback was found to be superior to oral diazepam, sham treatment, and laxatives; while surgical procedures such as partial division of the puborectalis muscle were more efficacious, the risks of adverse reaction, namely incontinence, were high. Thus, biofeedback therapy is the current gold-standard for the treatment of dyssynergia.[1] The success rate of biofeedback in correcting or improving the symptoms in patients with dyssynergia varies between 33% and 80%.[2] Difficulty arises in those in whom biofeedback is unsuccessful, as there is little, and conflicting, low quality evidence on alternative therapies.[2]

One further therapeutic option uses injection of Botulinum toxin type A (BTXA) into the puborectalis and/or external anal sphincter muscles. This is currently the second-line treatment for dyssynergic defaecation in whom biofeedback has failed. A systematic review in 2016[3] on the use of BTXA in patients with ‘anismus’, a term previously used to describe dyssynergic defaecation, demonstrated initial clinical improvement in symptoms in 77.4% of patients. Two of the seven studies were conducted on participants in whom biofeedback therapy had failed. Complications were reported in 7.4% of patients (0 to 22.6%) and included faecal incontinence, which was minor and transient,[3] posterior anal fissure, and rectal prolapse. The effect of BTXA was not permanent, with clinical improvement declining to 46% at four months after the injection. For this reason, several studies[4-6] offered repeated treatments.

The delivery of BTXA injection varied between studies and institutions in terms of dosage and position of injection, but all were performed via perianal or transanal approaches, often requiring sedation or anaesthesia. There are several disadvantages of this approach including cost (operating theatre utilisation) and risks associated with anaesthesia and infection from passing the needle through a contaminated[7] operative field. In addition, the injection site is defined blind by the surgeon’s finger (an issue of accuracy of injection and hazard of needle stick injury).

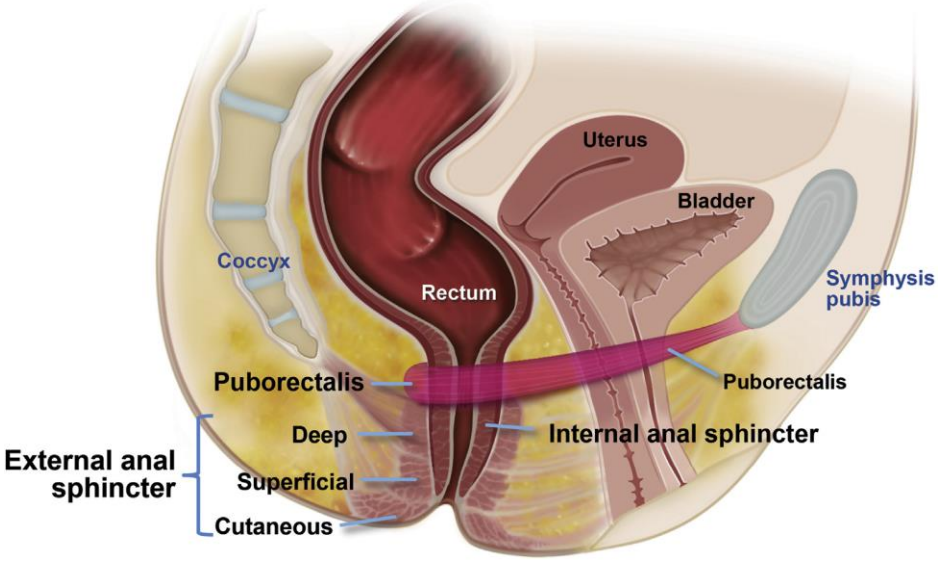
The proposed study aims to demonstrate the technical feasibility of an alternative approach to delivering BTXA injection in adult patients with dyssynergic defaecation. This novel technique injects BTXA into the puborectalis muscle percutaneously using an infracoccygeal approach under ultrasound guidance. This allows the procedure to be performed in an outpatient radiology setting without the need for any form of anaesthesia or analgesia. The injection

is performed in a clean operative field away from the anus, minimising risk of infection and the muscle can be clearly visualised (see below). These advantages will be particularly valuable in patients who require repeated procedures or those with multiple co-morbidities at high anaesthetic risk.

5.2 Rationale

The utilisation of BTXA in human is well established. This medication is licensed for use in focal spasticity[8] with well-established side-effects and interactions. Current evidence for the use of BTXA in dyssynergic defaecation is based on the conventional transanal approach, with report on efficacy and complications as previously stated.

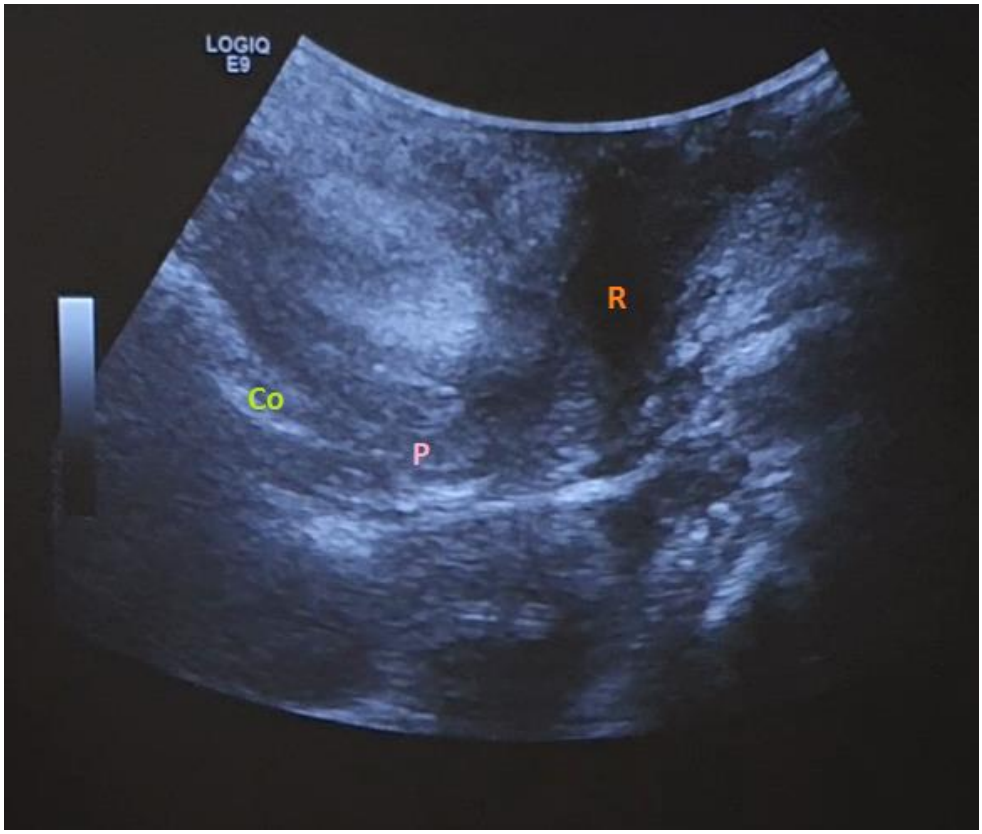
Figure 1. Anatomy of the anal canal and rectum



Rao et al, 2016[1]

The puborectalis (see Figure 1.) is easily accessible below the coccyx, and is the site for ultrasonic assessment in the paediatric population.[9] The identification of puborectalis muscle in the infracoccygeal position has not been described in the literature in the adult population. However, pilot imaging studies on a small number of non-obese subjects have been successful in easily identifying the puborectalis using ultrasound scan (see Figure 2.). This approach has the potential to allow accurate administration of BTXA injection under ultrasonic guidance in the outpatient setting without the need for anaesthesia or operating theatre utilisation.

Figure 2. Ultrasound scan of the puborectalis



P = Puborectalis, Co = Coccyx, R = Rectum (In prone position)

The general aim of this study is to demonstrate that percutaneous infracoccygeal BTXA injection is a valid alternative approach to transanal injection for the treatment of dyssynergic defaecation. Specifically, we will determine technical feasibility (including pilot proof of mechanism), patient acceptability, safety, and pilot efficacy outcomes for a future definitive trial.

5.3 Risks / benefits

5.3.1 Botulinum Toxin Type A related risks

The use of BTXA injection into the puborectalis and/or external anal sphincter muscles in patients with dyssynergic defaecation using the conventional transanal approach demonstrated initial clinical improvement in symptoms in 77.4% of patients, however in 46% of patients the effect was temporary and a repeat injection required.[3]

The general side-effects of BTXA are stated in the British National Formulary[8]. On review of current evidence (11 studies pertaining to 246 subjects), reported procedure specific side-effects relating to BTXA injection for the treatment of dyssynergic defaecation based on transanal injection include:

1. Temporary incontinence – faecal incontinence occurred in 17 cases (6.9%) from three studies[10-12] and flatus incontinence

occurred in 10 cases (4.1%) from two studies.[6, 12] The symptoms were minor and temporary in all studies.

2. Posterior anal fissure – reported in two patients (0.8%) from a single study[13]
3. Rectal prolapse – reported in a single patient (0.4%) from a single study[13]

5.3.2 Risks related to injection

Risks associated with ultrasound scan can be categorised as diagnostic errors and biological effects.[14] With regards to the risk of diagnostic errors, imaging the puborectalis using ultrasonography has been performed routinely as part of anorectal physiology studies but only using a transanal or perineal approach. The potential of diagnostic error (wrong muscle) using the percutaneous infracoccygeal approach is unknown but pilot imaging studies on a small number of healthy subjects demonstrate that it is easy to locate and obvious in terms of morphology. Further, volitional contraction can be used to demonstrate contraction under vision (see Figure 2).

Biological effects can be divided into thermal and mechanical effects. The National Council on Radiation Protection and Measurements (NCRP) report on the use of medical ultrasonography[15] concluded that there is no evidence to suggest that ultrasound has caused any adverse effects, based on human epidemiological studies.

The BTXA injection will be delivered through a narrow-gauge needle as used daily for muscle injections by a variety of health professionals worldwide. Slight soreness can be associated with injection, but risks of infection and bleeding are rare (<1/10,000).[16] We will record muscle activity (pilot proof of mechanism) using the same needle electrode avoiding further discomfort to the patient above that experienced from the injection alone.

Subcutaneous local anaesthetic infiltration with 1% lidocaine is routinely carried out for minor procedures. The general side-effects of lidocaine are stated in the British National Formulary.[8] The maximum dosage is 4mg/kg (0.4ml/kg of 1% lidocaine) or 30ml, whichever is smaller. The amount required for this procedure is 5ml.

5.3.3 Study benefits

Participants will add to the knowledge base for the treatment options for patients with dyssynergic defaecation. Though not certain, participants may also benefit from improvement in their constipation symptoms.

6. Study objectives

6.1 Primary objective

The primary objective of this study is to establish the technical feasibility of percutaneous infracoccygeal BTXA injection to puborectalis muscle as an alternative to transanal puborectalis muscle injection for the treatment of dyssynergic defaecation.

6.2 Secondary objective

- To assess safety of this technique
- To assess patient acceptability of this technique
- To derive pilot clinical efficacy data to inform future trials

6.3 Primary endpoint

In order to measure technical practicability, the physician delivering the therapy will be asked to complete a physician acceptability questionnaire at the end of each procedure. The questionnaire subjectively measures the physician's opinion of the procedure difficulty, patient's discomfort, whether or not the procedure is considered successful, and any procedure limitations.

Question/Statement	Scoring
1. Patient's body habitus	_____ kg _____ cm _____ BMI
2. Duration of procedure	_____ minutes
3. Puborectalis identified by USS	□ At rest □ Voluntary contraction
4. Puborectalis identified by EMG	□ At rest □ Voluntary contraction
6. Difficulty of procedure	□ Easy □ Moderate □ Difficult
7. Reason for your answer in question 5.	(Free text)
8. Patient was comfortable	□ Strongly agree □ Agree □ Neutral □ Disagree □ Strongly disagree
9. Procedure was completed successfully	□ Strongly agree □ Agree □ Neutral □ Disagree □ Strongly disagree
10. Procedure limitations	(Free text)

Technical practicability will also be measured objectively by the rate of successful identification of the puborectalis:

- Using ultrasound scan at rest and under voluntary contraction
- Using EMG at rest and under voluntary contraction

6.4 Secondary endpoint

6.4.1 Safety

Expected adverse event (AE) related to BTXA injection of the puborectalis include:

- Bruising at injection site
- Local skin reaction at injection site
- Pain at injection site
- Infection at injection site
- New or worsening faecal incontinence

Following the injection, any adverse event reported by the patients will be recorded on the adverse event (AE) form on the patient's eCRF using Research Electronic Data Capture (REDCap). This form will record the nature, severity, time of onset of, and treatment required for the AE. Patients are encouraged to self-report any adverse events as soon as possible by telephone. If no adverse events have been self-reported this will be confirmed with the patient at the end of every follow-up appointment as part of the follow-up procedure. In addition, at the time of first follow-up the injection site will be inspected for any signs of bruising, local skin reaction, or infection. At each follow-up, St. Mark's incontinence score will also be measured to allow detection of new or worsening incontinence, which is the main procedure specific risk associated with this procedure.

The severity of any adverse events will be classified according to the Clavien-Dindo classification[18] of surgical complications:

- Grade 1 – any deviation from normal post-operative course without need for pharmacological (antiemetics, antipyretics, analgesics, diuretics, and electrolytes are permitted), surgical, endoscopy, or radiological interventions
- Grade 2 – requiring pharmacological treatment other than those permitted in 1 (including blood transfusion and total parenteral nutrition)
- Grade 3 – requiring surgical, endoscopic, or radiological intervention
    - Grade 3a – not under general anaesthetic
    - Grade 3b – under general anaesthetic
- Grade 4 – life-threatening complication requiring intensive care management
    - Grade 4a – single organ dysfunction, including dialysis
    - Grade 4b – multi-organ dysfunction
- Grade 5 – death

Serious adverse events (SAE) will be recorded as above and will also be reported as described in the safety reporting section (see Section 16).

6.4.2 Treatment acceptability

Treatment acceptability will be measured objectively by the recruitment rate and subjectively using a patient acceptability questionnaire, which will be completed by the participant at the end of the procedure. The questionnaire measures patient's overall opinion of the procedure, level of

pain during treatment, satisfaction with the duration of the procedure, and willingness to undergo the procedure again.

Question/Statement	Scoring
1. The procedure was painful.	□ Strongly agree □ Agree □ Neutral □ Disagree □ Strongly disagree
2. The procedure was embarrassing.	□ Strongly agree □ Agree □ Neutral □ Disagree □ Strongly disagree
3. The procedure was comfortable	□ Strongly agree □ Agree □ Neutral □ Disagree □ Strongly disagree
4. The procedure duration was too long.	□ Strongly agree □ Agree □ Neutral □ Disagree □ Strongly disagree
5. What score corresponds best with your opinion of the treatment procedure? (10 = acceptable, 0 = unacceptable)	0 1 2 3 4 5 6 7 8 9 10 Unacceptable Neutral Acceptable
6. Reason for your answer in question 5.	(Free text)
7. Would you be willing to undergo this procedure again?	□ Yes □ No

6.4.3 Clinical efficacy

Subjectively improvement will be measured using the Cleveland Clinic Constipation Score (CCCS)[19] and Measure Yourself Medical Outcome Profile (MyMop)[20] assessment pre- and post- intervention.

As part of NHS follow-up care, the patients will undergo repeat anorectal physiology studies (anorectal manometry) to assess the need for further treatment. The post-procedure findings will be compared with pre-procedure findings to identify any changes.

This information will be helpful to make an estimate of the sample size and follow-up rate for future studies.

7. Study population

Patients will be recruited from referrals to the pelvic floor multidisciplinary team (MDT) meeting and those who fulfil the inclusion criteria will be invited to participate in the study. The duration for participation is 12 months.

7.1 Inclusion criteria

- Adult patients (age 18 – 80 years)
- Diagnosis of dyssynergic defaecation using ROME IV criteria[17].
  - The patient must satisfy diagnostic criteria for functional constipation and/or irritable bowel syndrome (IBS) with constipation
  - The IBS criteria includes recurrent abdominal pain, on average at least 1 day per week in the last 3 months, associated with 2 or more of the following: related to defaecation, associated with a change in

frequency of stools, or associated with a change in form (appearance) of stool.
- In IBS with predominant constipation (IBS-C) more than 25% of bowel movements are of Bristol stool form scale (BSFS) type 1 or 2 consistency, and less than 25% are of types 6 or 7.
- The functional constipation diagnostic criteria applies to those who do not meet the criteria for irritable bowel syndrome, whose stools are rarely loose without the use of laxatives, and must include 2 or more of the following: straining*, lumpy or hard stools (BSFS 1-2)*, sensation of incomplete evacuation*, sensation of anorectal obstruction/blockage*, manual manoeuvres to facilitate defaecation*, fewer than 3 spontaneous bowel movements per week
- During repeated attempts to defaecate, there must be features of impaired evacuation, as demonstrated by 1 of the following 2 tests: abnormal balloon expulsion test or impaired rectal evacuation by imaging**
- Inappropriate contraction of the pelvic floor as measured with anal surface EMG or manometry with adequate propulsive forces during attempted defaecation (as defined by age- and sex-appropriate normal values)
- Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

- Ability to understand written and spoken English.
- Ability and willingness to give informed consent.

* *More than 25% of defaecations.*

** *In our unit, imaging of rectal evacuation is performed using defaecography, and the assessment of pelvic floor contraction is assessed by evaluating the propulsive force, anorectal angle, and relaxation of the anal canal.*

7.2 Exclusion criteria

- Paediatric patients (age under 18 years)
- Diagnosis of defined structural or metabolic diseases that could cause constipation, such as Hirschsprung's disease, Parkinson's disease, multiple sclerosis, hypothyroidism (untreated), diabetic neuropathy, muscular dystrophy, motor neurone diseases, spinal injury leading to paraplegia, cauda equina syndrome
- Psychiatric or physical inability to comply with the study protocol (including e-diary assessments) at investigator discretion.
- Contra-indications to BTXA such as allergies, pregnancy (or intention to become pregnant during study period), breastfeeding, generalised disorders of muscle activity, myasthenia gravis
- Contra-indications to infracoccygeal injection at injection site such as infection or pressure sore, spina bifida, pilonidal disease, bleeding disorders (including therapeutic anticoagulation)
- Morbid obesity (BMI ≥ 40)
- Defunctioning loop or end stoma *in situ*
- External rectal prolapse

8. Study design

The overall design is of a single-centre, prospective, uncontrolled, open-label observational study. Patients diagnosed with dyssynergic defaecation, using Rome IV criteria, will be identified from weekly pelvic floor MDT and current waiting list for biofeedback therapy and invited to participate. BTXA injection is not offered as an alternative to biofeedback and does not preclude patients from receiving biofeedback therapy as per standard treatment as this is not a study of treatment efficacy.

All participants will undergo BTXA injection within 12 weeks of recruitment.

Data collection:

- Baseline data collection from patient's initial symptoms questionnaire and anorectal physiology report (pre-procedure).
- MYMOP questionnaire (pre-procedure and at final follow-up)
- Patient and physician procedural questionnaire to be completed at the end of the BTXA injection procedure (see Section 5.3 and 5.4).
- Cleveland clinic constipation score and St. Mark's incontinence score to be completed by the patient at each follow-up.
- Anorectal physiology report (post-procedure) for anorectal manometry results at first follow-up.
- Any adverse events reported by the patient will be recorded on an adverse event form (see Section 5.4).

Data analysis:

- Feasibility and efficacy outcomes will be extracted from the questionnaires and reports and recorded onto Research Electronic Data Capture (REDCap).
- Anonymised summary data will be exported to Excel and descriptive statistics (e.g. mean, confidence intervals of effect) used to present data for publication.

9. Study procedures

Recruitment

Patients diagnosed with dyssynergic defaecation, using Rome IV criteria, will be identified from the weekly pelvic floor MDT and current waiting list for biofeedback therapy. These patients will be screened against the inclusion and exclusion criteria. Patients will be continually recruited until 10 patients have undergone the procedure, including re-recruitment for drop-outs.

Visit 1: initial discussion

Eligible patients will be contacted by a member of the clinical team by telephone and invited to have a discussion about participating in the study. Following the initial discussion about the study with a member of the research team by phone, an information leaflet will be sent out. A minimum of 24 hours will be provided to allow the patient to consider the given information.

Visit 2: consent and baseline data

A second appointment will be arranged to obtain consent should the patient wish to participate in the study, which may be undertaken by an appropriately trained

member of the clinical or research team. Patient's original symptom questionnaire and anorectal physiology reports will be obtained to extract baseline data (CCCS, evacuation time and completeness, quality of expulsive force, opening of the anorectal angle, relaxation of the anal canal, as well as squeeze and push pressures). The patient will then complete CCCS, SMIS, and MyMop questionnaires.

Visit 3: BTXA injection

The BTXA injection will be scheduled by the radiology department within 12 weeks. The patient and radiologist carrying out the injection will complete a procedure-related questionnaire after the procedure. Ultrasound and EMG report on each patient will be obtained following the procedure. The patient will be asked to report any adverse events following the BTXA injection as soon as possible by phone or at follow-up.

Visit 4: first follow-up

The patient will attend first follow-up 4-6 weeks after the injection and complete the Cleveland Clinic constipation scoring (CCCS) as well as St. Mark's incontinence scoring (SMIS). They also undergo a repeat anorectal physiology tests.

Visit 5: second follow-up

The patient will be given the option of telephone, face-to-face, or electronic follow-up at 3 months following the injection and will complete the CCCS and SMIS. They will also be asked if they have experienced any adverse events.

Visit 6: final follow-up

This will take place at 6 months following the injection and will be similar to the second follow-up but the patient will also be asked to complete a MYMOP follow-up questionnaire, and to rank their level of satisfaction with the treatment using a satisfaction thermometer.

Visit	Study Stage	Data		Week	Carried out by	Setting
0	Recruitment	N/A		0	Research team	Pelvic Floor MDT
1	Initial discussion	N/A		1-4	Clinical/research team	Phone
2	Consent and baseline data	CCCS SMIS Anorectal physiology MYMOP		5-6	Clinical/research team	Outpatient clinic
3	BTXA injection	Patient questionnaire Physician questionnaire	Adverse events reporting	18	Radiologist	Outpatient Ultrasound
4	First follow-up	CCCS SMIS Anorectal physiology		22-24	Clinical/research team	GI physiology
5	Second follow-up	CCCS SMIS		30	Clinical/research team	Outpatient clinic/ phone/ online form
6	Final follow-up	CCCS SMIS MYMOP follow-up Satisfaction thermometer		42	Clinical/research team	Outpatient clinic/ phone/ online form

Study intervention (at visit 3):

Botulinum toxin type A injection (BTXA) – The intervention is an injection of 200 units of Botulinum toxin type A in to the puborectalis muscle under ultrasound guidance.

- In the prone position, the puborectalis muscle will be identified below the coccyx using ultrasound.
- After skin preparation using 70% Isopropyl Alcohol Pad, up to 5ml of local anaesthetic (1% lidocaine) an electromyography (EMG) needle will be inserted and the puborectalis muscle stimulated using a current to confirm correct needle position. Figure 3 demonstrates an example EMG trace on a healthy volunteer at rest (a) and under voluntary contraction (b)
- 200 units of BTXA (Botox, Allergan, Ireland) prepared in 2 ml of saline solution and drawn up using a 2ml syringe.
- 1ml (100 units) of BTXA solution is injected through the EMG needle into the puborectalis muscle to each side of the midline, achieving a total of 200 units.
- The needle is withdrawn, and the procedure is complete.

At the end of the procedure, the patient and physician both complete post-procedure questionnaires.

At any stage of the study, expected adverse events will be recorded on the patient's eCRF. If no adverse events have been self-reported this will be confirmed with the patient at the end of every follow-up appointment as part of the follow-up procedure. Serious or unexpected adverse events will be recorded and also reported according to research governance framework guidelines (see Section 14).

Patients can withdraw at any point in the study without the requirement to provide a reason. The data collected from the point of consent to the point of withdrawal will be kept for analysis of retention and follow-up rate, as well as incidents of adverse events depending on the stage at withdrawal. Such patients will return to routine care.

Figure 3a. EMG of puborectalis demonstrating tonic activity at rest

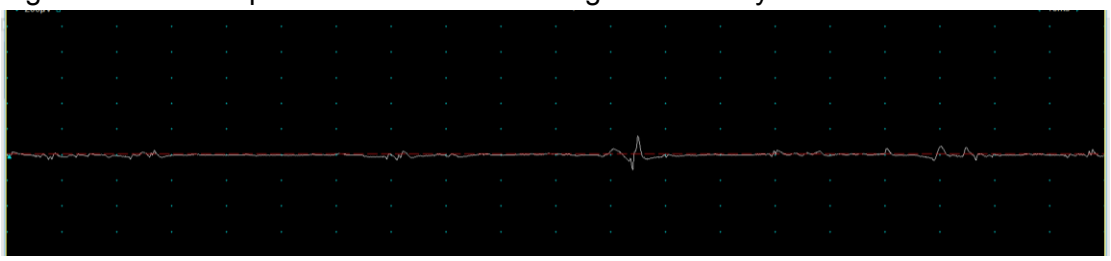
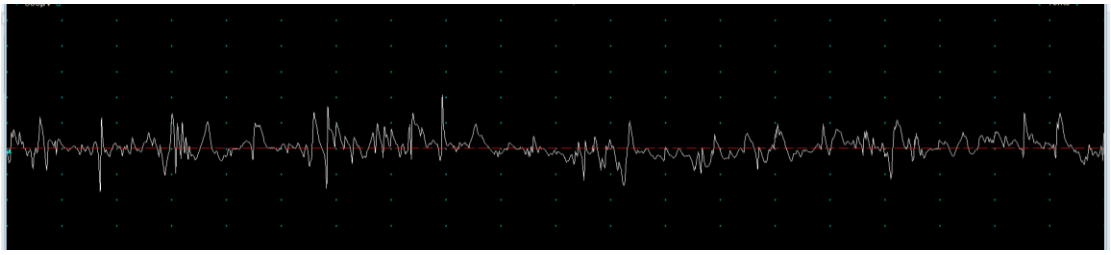


Figure 3b. EMG of puborectalis demonstrating voluntary contraction



10. Assessment and management of risk

Risk to the participants:

- The potential side-effects and expected AE's from Botulinum toxin type A injection are discussed in section 5.3.1 and 6.4.1, respectively. The potential risks to patients associated with the injection and routine NHS investigations are discussed in section 5.3.2 and 5.3.3, respectively. Any side-effects or AE's experienced by the participants will be assessed and treated by the clinical team and reported in accordance with the procedure outline in section 16 of this protocol.
- The questionnaires used in this study, in addition to routine care, are validated symptoms questionnaires (Cleveland Clinic constipation score, St. Marks Incontinence score, and MyMOP), a satisfaction thermometer, and a short post-procedure questionnaire. None of these contain any questions which are expected to cause mental or emotional harm.
- No financial loss for participants is anticipated as they will be compensated for travel expenses of up to £20 for each face-to-face appointment.

Risk to the clinician:

- There is no increased risk of needle stick injuries associated with this procedure in comparison with the current standard technique of BTXA injection (through the anal canal), which carries a higher risk of needle stick injury as it is guided by the administrator's finger and is not under direct vision.

11. Statistical considerations

This is a prospective, uncontrolled, open-label, observational study. Descriptive statistics are appropriate to present data. Data analysis on this basis will be supervised by the chief investigator.

11.1 Sample size

The sample size of 10 is a convenience sample (achievable in 12 months) and is not based on *a priori* calculations of statistical power. In the event of pre-procedure patient withdrawal, further recruitment will take place to achieve a total of 10 patients.

11.2 Method of analysis

Statistical analysis will not use hypothesis testing. Descriptive statistics will be used to summarise technical feasibility and other outcomes, including the proportion of patients who undergo successful BTXA injection where the puborectalis muscle was identified on ultrasound and on EMG before BTXA injection.

Qualitative summary of technical difficulties, patient satisfaction and reported adverse events will also be documented.

12. Ethics

This study is a non-CTIMP study using BTXA injection, which is an established treatment for dyssynergic defaecation, and will adhere to the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996), ICH Good Clinical Practice Guidelines (1996), current applicable local regulatory requirements, and REC conditions of approval.

Patients with dyssynergic defaecation on the waiting list for biofeedback therapy are offered BTXA injection using a novel approach, avoiding the need for general anaesthetic. It is not offered as an alternative to biofeedback and does not preclude patients from receiving biofeedback therapy as per standard treatment, as the aim of the study is not to assess efficacy of this treatment in isolation but to ascertain its acceptability to patients and physician. The additional symptom questionnaire and anorectal physiology tests performed at follow-up will assess the need for further treatment, which may be biofeedback therapy or repeat injection with BTXA, as part of ongoing NHS care.

12.1 Annual Safety Reporting

The CI will complete the Annual Progress Report (APR) to the REC and the sponsor using the HRA template at the end of the study.

13. Public Involvement

Prior to the commencement of this study, with Bowel Research UK through the Patient and Research Together (PaRT) initiation, public opinion on patient facing documents (information leaflet and consent) to develop informative and comprehensive patient literature for the study was sought. Public involvement remains the key focus of this study as its primary focus is on patients' opinion on this new treatment modality.

14. Data handling and record keeping

14.1Data management

Data will be handled in accordance with the Data Protection Act 2018 and Barts Health NHS Trust Information Governance policy. This study is performed on a single site.

Source data are kept in the original format. Electronic data (clinic letters, radiology and anorectal physiology reports, pregnancy test) are logged directly on the patient's electronic record. Original copies of physical data (questionnaires, case report forms, and consent forms) are kept in the site file, which is stored in a locked cupboard. Electronic case report forms are generated

electronically from the source data using REDCap and can be verified with the original records.

14.2Source data

Study Assessment	Source	Data Transfer
Screening and eligibility checklist	Pelvic floor MDT Electronic medical records	eCRF
Informed consent	Copy in site file and patient's notes	None
Patient questionnaires (including bowel symptoms questionnaire, CCCS, SMIS, MYMOP, post-procedure questionnaire, and satisfaction thermometer)	Patient	eCRF
Physician questionnaires	Physician	eCRF
Radiology report	Patient electronic records	eCRF
Anorectal physiology report	Patient electronic records	eCRF

14.3Confidentiality

Information related to participants will be kept confidential and managed in accordance with the Data Protection Act (2018), the General Data Protection Regulation (GDPR), NHS Caldecott Principles, the UK Policy Framework for Health and Social Care Research, the ICH Good Clinical Practice Guidelines (1996) and the conditions of Research Ethics Committee favourable opinion.

Patient identifiable information to be collected from the participants include:

- Full name
- Date of birth
- Hospital number
- Contact details

These will be used to contact the participants only and will not leave the study site without prior consent. All case report forms will be anonymised, and participants will not be identifiable in any future publications relating to this study.

Study data will be available to qualified members of the research team, auditors, the REC and any regulatory authorities as required by law.

14.4Record Retention and Archiving

The UK Policy Framework for Health and Social Care Research requires that research records are kept for 25 years after the project has completed. This single site study involve Barts Health NHS Trust patients, is undertaken by Barts Health NHS Trust staff. All research documentation (including consent forms and questionnaires) will be archived at the approved repository for long-term storage of local records, the Trust Corporate Records Centre.

15. Interventions and tools

15.1Techniques and interventions

The injection technique is described in section 9 under study intervention (at visit 3). There is no patent on this technique.

15.2Tools

The post-procedure questionnaire is included in section 6.4.2. Other validated questionnaires used in this study includes the Cleveland Clinic constipation score, St. Marks Incontinence score, MyMOP questionnaire, and a satisfaction thermometer.

15.3Medicinal product

Botulinum toxin type A (Botox, Allergan, Ireland)

- Indication: focal muscular spasm (of the puborectalis in dyssynergic defaecation)
- Licensing status: PL 00426/0119
- Dosing schedule: injection of 200 units once
- Route of administration: intramuscular injection (to puborectalis muscle)
- Source of Medicinal Product: Royal London Hospital pharmacy
- Storage and dispensing: product will be dispensed on the day of the procedure and stored in a refrigerator before use
- Contraindications:
    - Known hypersensitivity to BTXA, human albumin, sodium chloride
    - Presence of infection at the proposed injection site
- Side-effects:
    - Common or very common[8]: alopecia; asthenia; autonomic dysreflexia; bladder diverticulum; constipation; dizziness; drowsiness; dry eye; dry mouth; dysphagia (most common after injection into sternocleidomastoid muscle and salivary gland); ecchymosis (minimised by applying gentle pressure at injection site immediately after injection); eye discomfort; eye disorders; eye inflammation; fall; fever; gait abnormal; haematuria; headaches; hot flush; increased risk of infection; influenza like illness; insomnia; joint disorders; leukocyturia; malaise; muscle complaints; muscle weakness; musculoskeletal stiffness; nausea; neuromuscular dysfunction; oedema; pain; paresis; sensation abnormal; skin reactions; subcutaneous nodule; urinary disorders; vision disorders
    - Uncommon[8]: anxiety; coordination abnormal; depression; dysphonia; dyspnoea; facial paralysis; memory loss; oral paraesthesia; photosensitivity reaction; postural hypotension; speech impairment; taste altered; vertigo
    - Frequency not known[8]: abdominal pain; angioedema; angle closure glaucoma; appetite decreased; arrhythmia; diarrhoea; hearing impairment; hypersensitivity; myocardial infarction;

myopathy; nerve disorders; respiratory disorders; seizure; syncope; tinnitus; vomiting

- Procedure specific:
  - Temporary incontinence – faecal incontinence occurred in 17 cases (6.9%) from three studies[10-12] and flatus incontinence occurred in 10 cases (4.1%) from two studies.[6, 12] The symptoms were minor and temporary in all studies.
  - Posterior anal fissure – reported in two patients (0.8%) from a single study[13]
  - Rectal prolapse – reported in a single patient (0.4%) from a single study[13]

16. Safety reporting

All adverse events (AE) related to or thought to be related to the procedure will be recorded in the patient's eCRF using an adverse event form. This form will record the nature, severity, time of onset of, and treatment required for the AE. Severity of the AE is graded according to the Clavien-Dindo classification[18] (see Section 5.4)

16.1 Adverse Events (AEs)

An AE is any untoward medical occurrence in a participant to whom an intervention has been administered, including occurrences which are not necessarily caused by or related to that intervention. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with study activities.

16.2 Adverse Reaction (ARs)

An AR is any untoward and unintended response in a participant to an intervention. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the intervention qualify as adverse reactions. The expression 'reasonable causal relationship' means in general that there is evidence or an argument to suggest a causal relationship.

16.3 Notification and reporting of Adverse Events and Reactions

If the AE is not defined as serious, the AE will be recorded in the study documents and the participant followed up by the research team. The AE will be documented in the participants' source documents, the Case Report Form (CRF), and, where appropriate, medical records.

16.4 Serious Adverse Events (SAEs) or reactions

A serious adverse event (SAE) is defined as an untoward occurrence that:

- Results in death,
- Is life-threatening,
- Requires hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity,

- Consists of a congenital anomaly or birth defect, or
- Is otherwise considered medically significant by the investigator.

SARs will be reported to the REC where in the opinion of the CI the event was serious and:

- Related (it may have resulted from administration of any of the research interventions), and
- Unexpected (the type of event is not listed in the protocol or other Reference Safety Information as an expected occurrence).

16.5Notification and reporting of Serious Adverse Events

Serious Adverse Events (SAEs) that are considered to be 'related' and 'unexpected' will be reported to the sponsor within 24 hours of learning of the event, and to the REC within 15 days in line with the required timeframe.

16.6Urgent Safety Measures

The CI will take urgent safety measures if necessary to ensure the safety and protection of the clinical study participant from immediate hazards to their health and safety. The measures will be taken immediately. The approval of the REC prior to implementing urgent safety measures is not required. However, the CI will inform the sponsor and REC (via telephone) of this event immediately.

The CI will inform the REC in writing within 3 days, in the form of a substantial amendment. The sponsor (Joint Research Management Office (JRMO)) will be sent a copy of the correspondence with regards to this matter.

16.7Annual Safety Reporting

The CI will send the Annual Progress Report to the REC using the HRA template (the anniversary date is the date on the REC "favourable opinion" letter) and to the sponsor.

16.8Overview of the Safety Reporting responsibilities

The CI is the medical assessor on behalf on the sponsor and will review all events reported. The CI will ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements.

17. Monitoring and auditing

The sponsor or delegate retains the right to audit any study, study site, or central facility. Any part of the study may be audited by the funders, where applicable.

On-site monitoring is not required given the small study size and being conducted on a single site.

18. Trial committees

A small study management group (SMG) will be responsible for the delivery of the study, and will consist of:

- The trial CI: Prof. Charles Knowles (BHT/NBRC)
- Co applicant: Dr Mark Scott (BHT/NBRC)
- Clinical research fellow: Pam Chaichanavichkij (BHT/NBRC)
- Radiologist: Dr Niall Power (BHT)
- Neurophysiologist: Dr Abir Sanyal (BHT)
- Trial co-ordinator: N/A
- Data manager: N/A

19. Finance and funding

This study will utilise departmental funding as the procedure is a part of standard clinical care. Additional equipment specific to this technique (EMG needle), patient travel expenses, and cost of research staff is provided by Bowel Research UK small grant for the 12-months period of the study.

20. Indemnity

The insurance that Queen Mary University of London has in place provides cover for the design and management of the study as well as "No Fault Compensation" for participants, which provides an indemnity to participants for negligent and non-negligent harm.

21. Dissemination of research findings

Findings will be subjected to oral presentation in a specialist research meeting, reporting in an appropriate peer reviewed journal, and will also be disseminated through the Bowel Research UK website. It will also form part of the research fellow's PhD thesis.

22. References

1. Rao SS, Bharucha AE, Chiarioni G, et al. Functional Anorectal Disorders. Gastroenterology 2016.
2. Woodward S, Norton C, Chiarelli P. Biofeedback for treatment of chronic idiopathic constipation in adults. Cochrane Database Syst Rev 2014:Cd008486.
3. Emile SH, Elfeki HA, Elbanna HG, et al. Efficacy and safety of botulinum toxin in treatment of anismus: A systematic review. World J Gastrointest Pharmacol Ther 2016;7:453-62.
4. Shafik A, El-Sibai O. Botulin toxin in the treatment of nonrelaxing puborectalis syndrome. Dig Surg 1998;15:347-51.

5. Maria G, Brisinda G, Bentivoglio AR, et al. Botulinum toxin in the treatment of outlet obstruction constipation caused by puborectalis syndrome. Dis Colon Rectum 2000;43:376-80.
6. Maria G, Cadeddu F, Brandara F, et al. Experience with type A botulinum toxin for treatment of outlet-type constipation. Am J Gastroenterol 2006;101:2570-5.
7. Excellence NIfHaC. Surgical site infections: prevention and treatment (NG125). Volume 2019. NG125 ed, 2019.
8. Formulary TBN. Botulinum Toxin Type A. Volume 2019: MedicinesComplete, 2019.
9. Han TI, Kim IO, Kim WS, et al. US identification of the anal sphincter complex and levator ani muscle in neonates: infracoccygeal approach. Radiology 2000;217:392-4.
10. Zhang Y, Wang ZN, He L, et al. Botulinum toxin type-A injection to treat patients with intractable anismus unresponsive to simple biofeedback training. World J Gastroenterol 2014;20:12602-7.
11. Hompes R, Harmston C, Wijffels N, et al. Excellent response rate of anismus to botulinum toxin if rectal prolapse misdiagnosed as anismus ('pseudoanismus') is excluded. Colorectal Dis 2012;14:224-30.
12. You Y-TW, Jen-Yi; ChangChien, Chung-Rong; Chen, Jinn-Shiun; Hsu, Kuan-Cheng; Tang, Reiping; Yeh, Chien-Yuh. The Treatment of Outlet Obstruction Constipation. Farmosan Journal of Surgery 2001;34:3-10.
13. Ron Y, Avni Y, Lukovetski A, et al. Botulinum toxin type-A in therapy of patients with anismus. Dis Colon Rectum 2001;44:1821-6.
14. Abramowicz JS. Benefits and risks of ultrasound in pregnancy. Semin Perinatol 2013;37:295-300.
15. Measurements NCoRPa. Exposure Criteria for Medical Diagnostic Ultrasound: II Criteria Based on All Known Mechanisms. In: Nyborg WL, ed, 2002.
16. Gechev A, Kane NM, Koltzenburg M, et al. Potential risks of iatrogenic complications of nerve conduction studies (NCS) and electromyography (EMG). Clin Neurophysiol Pract 2016;1:62-66.
17. Lacy BE, Mearin F, Chang L, et al. Bowel Disorders. Gastroenterology 2016.
18. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
19. Agachan F, Chen T, Pfeifer J, et al. A constipation scoring system to simplify evaluation and management of constipated patients. Dis Colon Rectum 1996;39:681-5.
20. Paterson C. Measuring outcomes in primary care: a patient generated measure, MYMOP, compared with the SF-36 health survey. Bmj 1996;312:1016-20.

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