Is the time to complete bowel care quicker using transanal irrigation compared to standard bowel care in adults with Spinal Cord Disorders? A randomised controlled trial.

The TAI Study

CONFIDENTIAL

STATEMENT OF COMPLIANCE

This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (1) and the Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2) (2).

SIGNATURES

Co – ordinating Principal Investigator

Name: Professor Lisa Harvey

University of Sydney / Royal North Shore Hospital

Signature:  Date: 9th November 2020

Site Principal Investigator

Name: Louise Kelly

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Signature:  Date: 9th November 2020

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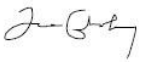
Signature:  Date: 9th November 2020

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Contents

PROTOCOL SYNOPSIS

Title	The TAI Study
Objectives	**Primary**: To determine the effect of transanal irrigation (versus standard bowel care) on time to complete toileting. **Secondary**: To determine the effect of transanal irrigation (versus standard bowel care) on the incidence of faecal incontinence, constipation and quality of life.
Study Design	Pragmatic, single blinded, randomised controlled trial
Planned Sample Size	24 (12 in each group)

Selection Criteria	People will be eligible for inclusion if they:
	• have sustained a spinal cord injury more than 6 months prior or have Spina Bifida
	• have a Neurogenic Bowel Dysfunction Score (3) ≥ 3
	• are aged 18 years or over at the time of consent
	• are willing to participate in the trial
	• have been recommended to trial transanal irrigation by a clinician because they spend more than 30 minutes on toileting AND ANY ONE OF THE FOLLOWING:
	  ○ had more than 1 episode of faecal incontinence per month
	  ○ had a Bristol stool chart result of <3 or >6 for more than 3 cycles of bowel care
	  ○ experienced abdominal symptoms such as bloating/cramping
	  ○ experienced inconsistency with defaecation
	  ○ experienced rectal symptoms (bleeding haemorrhoids, rectal prolapse, fissures etc)
	  ○ experienced autonomic dysreflexia in response to bowel care

Study Procedures	All eligible people living in the community will be invited to participate. If agreeable they will have baseline data collected and then be randomised into treatment group (transanal irrigation) or control group (standard bowel care) for six weeks. Transanal irrigation involves administration of approximately 400mL of luke-warm water via the rectum using a commercialised 'kit'. This kit includes a rectal catheter, tubing and a reservoir to hold the water. The principle is to 'flush' the lower colon clear of stool to avoid constipation and incontinence. Standard bowel care involves the use of micro enemas/suppositories, digital stimulation of the rectal sphincter, manual evacuation of stool or a combination of enemas/suppositories and digital stimulation. Outcomes will be assessed at 6 weeks post intervention by blinded assessors.
Statistical Procedures	24 participants will be required to detect a between group difference of 20 minutes on the primary outcome. This assumes

	an α level of 0.5%, a SD of 18 minutes and a correlation between pre and post values of 0.4. Regression models will be used to determine between group differences (and 95% CI). Results will be interpreted with respect to the minimally worthwhile treatment effect.
Duration of the study	The trial is expected to take approximately 2 years to complete. We anticipate the recruitment will commence in March 2021.

GLOSSARY OF ABBREVIATIONS

ABBREVIATION	TERM
ANZCTR	The Australian and New Zealand Clinical Trials Registry
CONSORT	Consolidated Standards for Reporting Trials
CRF	Case Report Forms
JWCRR	John Walsh Centre for Rehabilitation Research, University of Sydney and Northern Sydney Local Health District, Australia
NBD	Neurogenic Bowel Dysfunction
SB	Spina Bifida
SCD	Spinal Cord Disorders
SCI	Spinal Cord Injury
SBC	Standard Bowel Care
TAI	Transanal Irrigation. Introduction of water into the rectum and lower colon.

1. STUDY MANAGEMENT

1.1 Co-ordinating Principal Investigator

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1.4 Sponsor

University of Sydney

1.5 Funding and resources

This trial is funded by a philanthropic donation and a grant from icare.

2. INTRODUCTION AND BACKGROUND

2.1 Background Information

Spinal Cord Injury (SCI) and Spina Bifida (SB) are two common causes of Spinal Cord Disorders (SCD). Both conditions can cause neurogenic bowel dysfunction (NBD) (4, 5). The severity of NBD is linked to the level of injury and 'completeness' of the lesion (6). Primary symptoms of NBD include constipation, incomplete bowel emptying and faecal incontinence (5).

A major goal of bowel care for individuals with SCD is timely and effective defaecation. This relies upon management of multiple factors. In New South Wales (NSW) and Queensland (QLD), most people with SCD are placed on a 'standard bowel care' program (7) which consists of:

- dietary management plus additional aperients to titrate stool consistency
- rectal medications (i.e. enema/suppositories) where appropriate
- digital stimulation or digital evacuation of stool
- stimulate the gastro-colonic reflex by eating breakfast before bowel care (8), and
- perform toileting at around the same time each day / second day.

Irrespective of these measures, bowel care can take a considerable amount of time and there are numerous reports in the literature to suggest that the length of time spent on bowel care can increase with time since injury (9). For example, people with NBD can spend over 90 minutes every day emptying their bowels. In addition, prolonged toileting can lead to complications such as haemorrhoids, anal fissures, dilation of the sigmoid colon, autonomic dysreflexia and pressure injuries. All can have a significant impact on physical and psychosocial wellbeing (10-14) as well as the ability to engage in vocational, recreational and social activities (15, 16). People with SCD rate bowel care as one of the most disabling aspects of SCD and of more importance to them than the inability to walk (4, 17). A particular aspect that people with SCD find most challenging is the time it takes to complete their bowel care routine (15, 18, 19) therefore it is a very disabling sequalae of SCD that requires attention.

Transanal irrigation (TAI) has been present in the Australian health care context for approximately twenty years with the biggest uptake in the paediatric and Spina Bifida population (20-22). It involves introduction of a large volume of luke - warm water (400 – 1000mL) into the rectum/lower colon via a rectal catheter which is held in place via an inflatable balloon. There are also cone shaped applicators instead of catheters. Currently, there are 3 companies that have TGA approval to provide TAI in Australia; Coloplast (Peristeen ®), Mediplast (Navina ™) and Sayco (Aquaflush®). It has only been a recent change in funding for people with chronic disability that

has made this modality of bowel management more accessible to adults with SCD and thus a feasible option for exploration as an alternative bowel care routine, particularly for those people who are experiencing complications related to bowel care or spending a prolonged time on toileting. However, there are very little accurate data upon which to guide clinical practice. In particular, there are no rigorous data to indicate whether TAI results in a clinically meaningful reduction in the time people with SCD spend on bowel care.

2.2 Research Question

Is the time to complete bowel care quicker using transanal irrigation compared to standard bowel care in adults with spinal cord disorders?

2.3 Rationale for Current Study

Bowel care is time consuming, burdensome and a negative experience for many people who have SCD. Several studies have investigated the use of TAI in populations suffering NBD in Europe and Asia however, they have mainly focussed on safety, cost-effectiveness, compliance and quality of life outcomes (23-29). In a recent Cochrane Review, Coggrave et al reported that there was evidence in favour of TAI over conservative management (standard bowel care) however, the authors concluded that it was not possible to make recommendations on best bowel care practices using any of the studies that were included in the review due to the poor methodology of the included studies (15).

One important randomised clinical trial examined whether TAI improves constipation, faecal incontinence and NBS (30). Even though it wasn't an end point, the authors concluded that time sitting on the toilet was less in the TAI group (n= 43, mean = 49.1 mins, SD = 46.8) compared to the standard care group (n=37, mean = 30.8 mins, SD = 18.9). There are several issues with these data. The most obvious is that time spent sitting on the toilet was not reported as an outcome measure per se. Instead it was reported along with other incidental data (none of which was clearly identified as outcomes measures). The large amount of incidental data (in addition to the clearly articulated set of outcomes) increases the type I error rate and the resultant possibility of spurious findings. In addition, the data were obtained via a questionnaire relying upon participants' self-report. There are two problems with this. Firstly, the participants' recall may not have been accurate, and secondly, the participants were not blinded so their reports may have been biased and influenced by their expectations of treatment effectiveness. Irrespective of these concerns, the point estimate for time to toileting was very imprecise as reflected by the wide 95% confidence interval (mean between group difference = 18.3 mins, 95% CI = 3.0 to 33.6 favouring TAI[*]). A possible treatment effect as small as 3 minutes may not be clinically meaningful. That is, such as small reduction may not justify the time and cost of TAI. We believe that the most likely reason that the authors of this original study were unable to attain a more precise estimate of the treatment effect was because they included many participants in whom TAI was being prescribed for problems other than time spent on bowel care. Consequently, many participants did not spend an overly extended period of time on bowel care and TAI therefore may not have reduced the time these participants spent on bowel care. For this reason, we want to investigate the effect of TAI on time to complete bowel care in people with SCD where this is

[*] These data were not provided in the original paper but instead calculated from the provided mean, n, SD for each group.

their main problem. In particular, we want to attain a more precise estimate of the effect of TAI on time to complete bowel care. This will help us answer the question as to whether TAI has a clinically meaningful reduction on time spent on bowel care in individuals presenting with this problem.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary aim of this study is to determine if TAI reduces time spent on toileting (as determined by blinded assessors) in adults with chronic SCD living in NSW/QLD.

3.2 Secondary Objectives

The secondary objectives are to determine if TAI in adults with chronic SCD living in NSW/QLD:

- reduces time spent on toileting (as determined by participants with the use of diaries)
- reduces constipation
- reduces faecal incontinence
- improves quality of life
- improves perceptions of effectiveness of bowel care routines
- reduces the burden of bowel care

4. STUDY DESIGN

4.1 Type of Study

A pragmatic, prospective, community based, single blinded randomised controlled trial.

4.2 Study Design

The trial will be a community based, randomised controlled trial. All eligible participants will be invited to participate. Participants will be randomised to either transanal irrigation (TAI) (intervention) or standard care (control).

Participants allocated into the intervention group will commence transanal irrigation including training and support from a Registered Nurse with experience in the procedure. All aspects of transanal irrigation will be individualised to the participant as is current practice when establishing a routine with TAI. Participants allocated into the control group will continue with their current bowel care routines.

The primary outcome will be time to complete routine bowel care at six weeks.

Participants will not be blinded to their group allocation because of the nature of the system and the need for participant / carer training, however, the assessor will be blinded to group allocation.

All participants will continue to receive all non-rectal interventions that constitute ‘usual or standard care’. This includes the use of oral aperients, adequate fluid intake, and appropriate dietary intake, timing of bowel care and pr checks and digital stimulation as required (31).

All design features important for minimising bias will be adhered to and the trial will be registered with The Australian and New Zealand Clinical Trials Registry (ANZCTR). The minimally worthwhile treatment effect and statistical analyses will be set prior to the commencement of the trial in accordance with best practice. All relevant details enabling the compilation of a CONSORT flow diagram will be recorded and reported.

4.2 Number of Participants

Twenty four.

4.3 Study sites

The study is community based; therefore, participants will be recruited from either the spinal outpatient departments of Royal North Shore Hospital and Prince of Wales Hospital or via the community.

All study nurses will receive education and training on the set up and use of the 3 main transanal irrigation systems and this will be supported with a procedural document to ensure consistency.

It is anticipated that 12 participants will be recruited from New South Wales and 12 participants from Queensland.

4.4 Expected Duration of Study

The trial is expected to commence on 1st March 2021, with recruitment expect to take up to 24 months. Assuming recruitment continues until 1st March 2023, the final data collection will occur mid April 2023.

4.5 Primary and Secondary Outcome Measures

One primary and 6 secondary outcomes will be used. Most outcomes will be collected on two occasions at baseline and at six weeks post randomisation. The exceptions are two outcomes which will be collected on two occasions but at six weeks only: The *Global impression of change and Burden of treatment*. The other exception is the *time to complete bowel care (participant determined)*. This outcome will be collected using diaries over the week preceding the baseline and six week assessments.

Primary outcome:

1. *Time to complete bowel care (assessor determined)*: The time from commencement of the enema/irrigation administration procedure to completion of faecal elimination as defined by an empty rectum on per rectum (pr) check. This will be assessed 4 times: on two occasions (2 separate days) at baseline (after randomisation) and on two occasions at week 6 (upon completion of the trial). The two measurements taken at each time point will be averaged to attain one score for each time point.

Secondary outcomes:

1. Time to complete bowel care *(participant determined)*: The time from commencement of the enema/irrigation administration procedure to completion of faecal elimination as defined by an empty rectum on per rectum (pr) check. The participants will be required to use a stopwatch /timer to time bowel care on two occasions (2 separate days) at baseline (after randomisation)

and on two occasions (2 separate days) at week 6 (upon completion of the trial). These occasions will be on days that blinded assessment will NOT occur. Participants will be required to enter the bowel care times into a diary. The two measurements taken at each time point will be averaged to attain one score for each time point.

2. *Severity of constipation*: This outcome captures the severity of constipation. It will be measured using the Cleveland Clinic Constipation Scoring System (CCCSS) (32). This is an 8–item self-report questionnaire. Participants are required to respond to questions such as *"completeness: Feeling incomplete evacuation:* on a Likert scale (0-4) anchored with the following words *"never", rarely", "sometimes", "usually", "always"*. Total scores range from 0-30 (30 being the most severe symptoms of constipation). This will be assessed 4 times: twice prior to commencing the trial (baseline) and twice in week 6 (upon completion of the trial). Measurements will be averaged to attain one score for each endpoint.

3. *Frequency of unplanned bowel evacuations*: This outcome captures faecal incontinence outside of regular bowel care. It will be measured using the Vaizey (St Mark's) Faecal Incontinence Scale (33). This is a 7-item self-report questionnaire with an overall score ranging from 0-24 (0 = perfect continence, 24 being totally incontinent). Participants will be required to respond to questions such as *"in the past 4 weeks I had incontinence of solid stool"* on a Likert scale (0-4) anchored with the following words *"never", "rarely", "sometimes", "weekly", "daily"*. This will be assessed 4 times: twice prior to commencing the trial (baseline) and twice in week 6 (upon completion of the trial). Measurements will be averaged to attain one score for each endpoint.

4. *Spinal Cord Injury Quality of Life (SCI QoL) – Bowel Management Difficulties:* (34) This outcome captures quality of life due to bowel management difficulties. It will be measured using the SCI QoL. This is a 9-item self-report questionnaire with an overall raw score ranging from 9 to 45. Participants are required to respond to statements such as *"I was frustrated by repeated bowel accidents"* on a Likert Scale (1-5) anchored with the following words: *"not at all", "a little bit", "somewhat", quite a bit" and "very much"*. This will be assessed 4 times: twice prior to commencing the trial (baseline) and twice in week 6 (upon completion of the trial). The total raw score will be converted into a T score (see, Table 9 (34)) where a higher score is indicative of a worse outcome. Measurements will be averaged to attain one score for each endpoint.

5. *Global impression of change in bowel function (Participant reported)* (35): This outcome captures participants' perception of how much their bowel function has changed over the last six weeks. It will be measured using a 15-point Scale. Scores will be anchored at each end from -7 *"very much worse"* 0 *"no change"* to 7 *"very much better"*. Participants will be asked:

> *Do you think there has been a change for better or worse in any aspects of your bowel function or bowel routine over the past 6 weeks? Please rate from -7 to 7 where -7 indicates "very much worse " 0 indicates "no change" and 7 indicates " very much better".*

This will be assessed twice in week 6 (upon completion of the trial). Measurements will be averaged to attain one score for this endpoint.

6. *Burden of treatment questionnaire.* This outcome is designed to measure the level of burden participants feel around the treatment for their neurogenic bowel dysfunction over the past 6

weeks. It will be measured using an 11-point Likert Scale (0-10) anchored at each end from *"not at all bothersome"* to *"extremely bothersome"*. Participants will be asked:

> *How bothersome have you found managing your bowel routine over the last 6 weeks? Please rate on the below scale from 0 to 10 where 0 indicates "not at all bothersome: and 10 indicates "extremely bothersome"*.

This will be assessed on two occasions at week 6 (upon completion of the trial). Measurements will be averaged to attain one score for each endpoint.

5. STUDY TREATMENTS

5.1 Treatment Arms

5.1.1 Description

Regardless of which trial arm participants are allocated to, they will continue to receive all other non-rectal aspects of a 'bowel routine' that constitutes 'standard care'. This includes dietary and fluid management, the use of timed toileting (eliminating at the same time each day), pr checks prior to commencing and at the end of bowel care and the use of aperients titrated by stool consistency documented using the Bristol stool chart.

Intervention Group

The participant will use transanal irrigation daily or second daily (depending upon his/her current bowel routine) for a period of 6 weeks. Bowel care will be provided by the participant or carers trained in use of the irrigation system. Bowel care will occur at the usual time that s/he attends to his/her toileting and all participants will use the system whilst seated on a commode chair over their toilet.

Control Group

The participant will continue to use rectal medication / procedures as usual for a period of six weeks. Bowel care will be provided by the participant or carers. Bowel care will occur at the usual time that s/he attends to his/her toileting and all participants will have bowel care whilst seated on a commode chair over their toilet.

5.1.2 Dosage and Route of Administration

Intervention Group

All participants will commence on 400mL of luke-warm water (as per the manufacturer's instructions) delivered via the rectum. Water volume will be titrated up to a maximum of 1 L (as per the manufacturer's instructions).

Control Group

All participants will continue with their usual dosage of micro enemas or suppositories. This is typically 5mL of Sodium citrate dihydrate, sodium lauryl sulfoacetate and sorbitol micro enema

(Microlax®) or 1-2 glycerol suppositories. Micro enemas and suppositories are administered via the rectum.

6 PARTICIPANT ENROLMENT AND RANDOMISATION

6.1 Recruitment

Recruitment will occur from the spinal outpatient department at Royal North Shore Hospital and directly from the community. Participants will be pre-screened by their Primary Nurses / Treating Clinicians. If a potential participant is deemed appropriate for the trial, the participant will be asked to provide verbal consent for his/her contact details (name and phone number) to be shared with the Site Principal Investigator. The Site Principal Investigator will then contact the potential participant within 2 weeks to further explain the trial and ensure the participant is eligible. If the participant is eligible and interested in being involved, he/she will be provided with a Participant Information Sheet. A log will be kept of all people referred to the trial regardless of whether a potential participant is eligible and/or agrees to participate.

6.2 Eligibility Criteria

6.2.1 Inclusion Criteria

People will be eligible for inclusion if they:

- sustained a spinal cord injury more than 6 months prior or have Spina Bifida
- have a Neurogenic Bowel Dysfunction Score (3) ≥ 3
- are aged 18 years or over at the time of consent
- are willing to participate in the trial
- have been recommended to trial transanal irrigation by a clinician because they spend more than 30 mins on toileting AND ANY OF THE FOLLOWING:
  - had more than 1 episode of faecal incontinence per month
  - had a Bristol stool chart result of <3 or >6 for more than 3 cycles of bowel care
  - experienced abdominal symptoms such as bloating/cramping
  - experienced inconsistency with defaecation
  - experienced rectal symptoms (bleeding haemorrhoids, rectal prolapse, fissures etc)
  - experienced autonomic dysreflexia in response to bowel care

6.2.2 Exclusion Criteria

People will be excluded if:

- they are unable to co-operate (e.g. a serious medical condition, cognitive impairment, drug dependency, psychiatric illness, and behavioural problem)
- they are unable to speak sufficient English to provide informed consent
- they are currently using bisacodyl suppositories or enemas as the primary method for managing bowel care routine.
- transanal irrigation is contraindicated for use (36) for any of the following reasons:
  - anal / rectal stenosis
  - active inflammatory bowel disease
  - acute diverticulitis
  - colorectal cancer

- within 3 months of rectal surgery
- within 4 weeks of endoscopic polypectomy
- ischaemic colitis
- current or planned pregnancy
- long term steroid therapy
- radiotherapy to the pelvis
- dense sigmoid disease
- on anticoagulants (warfarin, apixaban, rivaroxaban, dabigatran)

6.3 Informed Consent Process

Potential participants will be given a copy of the Participant Information Sheet to review, and will be informed both verbally, and in writing (via the Participant Information Sheet) that their participation in the trial is entirely voluntary and it will not affect their current or future relationships with the treating clinicians or the Principal Investigators. Participants will be encouraged to ask questions regarding the trial or discuss with family and friends before consent is given. Once the essential trial information has been provided, the participants will be asked to give informed consent to participate in the trial by signing the Consent Form in the presence of a witness. These forms will be dated and retained by the Investigator at the site where all research data will be kept, and a copy will be provided to the participant. Any ongoing dependent relationship between clinicians and the participant will not be affected if a participant chooses to withdraw after consent has been given. It is most unlikely that the Principal Investigators and participants will be in any ongoing dependent relationship.

6.4 Enrolment and Randomisation Procedures

Participants will be enrolled into the study after the informed consent process has been completed. Because half of the participants will be randomised into the control group, procurement and training of the preferred TAI system will occur *prior* to randomisation for each participant so that the control arm will be able to commence TAI as soon as they complete the study if they wish to. The investigator responsible for collecting the baseline data will check that each participant meets the inclusion criteria. They will collect and confirm all demographic information including date of birth, sex, details about the injury/condition, including date of injury as well as a SCI bowel function data set. Baseline data on the primary and 4 of the 6 secondary outcome measures will be also be collected prior to randomisation.

A secure random-allocation schedule will be computer-generated prior to commencement of the trial by an independent person and kept at a central off-site location. The randomisation schedule will be blocked (1:1) to ensure equal numbers of participants are randomised to the treatment and control arms. A participant will be entered into the trial when baseline details are logged, and the allocation is provided. At this point, the participant will receive a study number, and this will be documented on all study documents.

6.5 Blinding Arrangements

It is not possible to blind the participants, study nurses or carers to allocation. However, all assessors will be blinded. Additionally, all Associate Investigators will remain blinded. To ensure this, the study nurses, participant and / or carers delivering the bowel care will be asked not to discuss any aspects of their bowel care with the associate investigator(s). The success of blinding for the assessor/s will be checked following the 6-week assessment.

6.6 Breaking of the Study Blind

6.6.1 On Study

Blinding will be broken if deemed necessary for safety. In addition, after the blinded assessor collects all assessments at six weeks, s/he will ask participants some open-ended questions that will invariably unblind the assessor.

6.6.2 Following Completion of the Study

Blinding will only be broken upon completion of locking of the database and completion of the statistical analysis.

6.7 Participant Withdrawal

6.7.1 Reasons for withdrawal

The following categories of withdrawal are possible for each participant:

Withdrawal from the trial and lost to follow-up – participant decides to withdraw from the trial and any further assessments.

Withdrawal from the trial – participant decides to withdraw from the trial but agrees to further assessments.

Lost to follow up – participant does not notify trial staff the s/he wishes to withdraw from the trial and cannot be contacted, therefore follow up assessments do not occur.

The consent form will advise participants that all data will be used if they are lost to follow up or choose to withdraw from the trial. However, there will be an option in the withdrawal of consent form to revoke consent for the use of data already collected.

The date and reason for any type of withdrawal will be recorded in the participant source file and on the completion page of the CRF. Where a participant exercises his/her right to discontinue participation in the trial, s/he will still be invited to participate in the follow-up assessment. Missing data will not be imputed. If >5% of data are missing, a sensitivity analysis will be done to determine the effect of the missing at random assumption.

6.7.2 Replacements

Withdrawals or losses after randomisation will not be replaced.

6.8 Trial Closure

The trial will not be stopped for futility but will be stopped if there are reasons for concern about safety. All Adverse and Serious Adverse Events will be reviewed by a safety monitoring board with an independent medical monitor, Dr Lianne Nier who will be consulted if there are any reasons for concern. There will be no follow-up of participants after their 6-week assessment.

6.9 Continuation of Therapy

All participants in the intervention group will be free to continue with the therapy if they are happy with the product and procedure. Participants in the control group will be free to pursue TAI with their treating clinicians but this will not be supported or supervised by the trial.

7 STUDY VISITS AND PROCEDURES SCHEDULE

	Screening and recruitment	Assessment at baseline		Intervention	Assessment at 6- weeks post randomisation	
Procedure Schedule	**-6 to -1 week**	**-7 to 0 days**		**Week 1 - 6**	**Week 7**	
Protocol Activity:		**1st visit**	**2nd visit**		**1st visit**	**2nd visit**
Informed Consent	✓					
Eligibility Checklist	✓					
Demographic details	✓					
Procure TAI Device	✓					
Training on how to use TAI	✓					
Randomisation			✓			
Adverse Events Check		✓	✓	✓✓✓✓✓✓	✓	✓
Outcome measures: Neurogenic Bowel Dysfunction Score		✓	✓		✓	✓
Time to complete bowel care (assessor)		✓	✓		✓	✓
Time to complete bowel care (participant)		✓	✓	✓✓		
CCCSS		✓	✓		✓	✓
St Mark's Scale		✓	✓		✓	✓
SCI-QOL, BMD		✓	✓		✓	✓
Global Impression of Change					✓	✓
Blinding question Assessor		✓	✓		✓	✓
End of Study checklist						✓

8 CLINICAL AND LABORATORY ASSESSMENTS

This trial does not involve collection of human tissue, blood or body fluids.

There will be a mix of demographic data and outcome measure assessments collected by the same blinded assessor during the face to face assessments at baseline and 6 weeks post randomisation as per study visit and procedures schedule.

9 ADVERSE EVENT REPORTING

9.1 Definitions

9.1.1 Adverse Event (AE)

An adverse event (AE) for medicines, also referred to as an adverse experience, is any untoward medical occurrence in a participant administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (37).

9.1.2 Adverse Reaction (AR)

An Adverse Reaction (AR) is any untoward and unintended response to an investigational medicinal product related to any dose administered to a participant. All adverse events determined to have a reasonable possibility to have been caused by the medicinal product are considered to be adverse reactions (37).

9.1.3 Adverse Device Effect (ADE)

An Adverse Device Effect (ADE) is any adverse event related to the use of an investigational medical device. It includes events resulting from insufficient or inadequate Instructions for use, or any malfunction of the investigational medical device. It also covers any event resulting from use error or from intentional misuse of the investigational medical device (37).

9.1.4 Device Adverse Event (DAE)

A Device Adverse Event (DAE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users or other persons, whether or not related to the investigational medical device. It includes events related to the procedures involved in using the device. A DAE for users or other persons is restricted to events related to the investigational medical devices (37).

9.1.5 Expected Occurrence (EO)

An Expected Occurrence (EO) is an adverse event or reaction that is highly prevalent in people with chronic SCD and very unlikely to be related to the clinical trial intervention. This includes urinary incontinence, urinary tract infection, respiratory infection, constipation, faecal incontinence, haemorrhoids, autonomic dysreflexia, pressure injury, hypotension, and spasticity. These will only be reported as adverse events if the investigator considers their occurrence to be a result of participation in the clinical trial.

9.2 Assessment and Documentation of Adverse Events

All AEs will be evaluated by seriousness, causality and expectedness (38). All EOs will be identified on the Adverse Event/Reaction case report form (CRF) to differentiate between known, unexpected AE/ARs and ADE/DAEs. The Principal Coordinator along with Site Co-ordinators will conduct safety monitoring and reporting requirements for this study in accordance with the attached NSW Health policy directive i.e. only report SSI's to the HREC. Adverse event reporting will be included on the annual report to the NSLHD HREC.

10 SERIOUS ADVERSE EVENT REPORTING

10.1 Definitions

10.1.1 Serious Adverse Event (SAE) / Serious Adverse Reaction (SAR)

A Serious Adverse Event (SAE) is any unforeseen medical event that occurs during clinical research that:

- results in participant death
- is life-threatening to the participant
- requires the inpatient hospitalisation or prolongation of existing hospitalisation for the participant leads to the participant having a persistent or significant disability/incapacity.
- leads to a congenital anomaly or birth defects.

In the context of a SAE/SAR definition, the term life-threatening refers to an event in which the participant was at risk of death at the time of the event, not an event that hypothetically might have caused death if it were more severe. Medical and scientific judgement should be exercised in deciding whether an adverse event/reaction should be classified as serious. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above will also be considered serious (37).

10.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Suspected Unexpected Serious Adverse Reaction **(**SUSARs) is any adverse event that is suspected to be related to an investigational medicinal product and that is both unexpected and serious. This includes a serious adverse event for which there is some degree of probability that the event is an adverse reaction to the administered drug and the adverse reaction is unexpected. It also captures serious events NOT outlined in the study protocol or information sheet (37).

10.1.3 Serious Adverse Device Effect (SADE)

A Serious Adverse Device Effect (SADE) that has resulted in any of the consequences characteristic of a serious adverse event such as:

- results in participant death
- is life-threatening to the participant
- requires the inpatient hospitalisation or prolongation of existing hospitalisation for the participant leads to the participant having a persistent or significant disability/incapacity
- leads to a congenital anomaly or birth defects (37).

10.1.4 Unanticipated Serious Adverse Device Effect (USADE)

An Unanticipated Serious Adverse Device Effect (USADE) is an effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (37).

10.1.5 Anticipated Serious Adverse Device Effect (ASADE)

An Anticipated Serious Adverse Device Effect (ADADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report (37).

10.1.6 Significant Safety Issue (SSI)

A Significant Safety Issue (SSI) is an event that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial (38).

10.2 Eliciting Serious Adverse Event Information

All participants and trial nursing staff will be provided with written definitions for SAE/SADE, SUSAR, USADE and SSI with trial office phone number for making contact in the event that this occurs during the trial. The details will be outlined on the Assessment and Documentation of Serious Adverse Events Form.

All SAEs will be evaluated by seriousness, causality and expectedness (38). All EOs will be identified on the Serious Adverse Event/Reaction case report form (CRF) to differentiate between known, unexpected SAE/SARs, SUSARS, and ASADE/USADEs. Additionally, the Investigators will conduct safety monitoring and reporting requirements for this study in accordance with the NSW Health policy directive PD2017_039 inclusive of any SSIs (38).

11 STATISTICAL METHODS

11.1 Sample Size Estimation

The minimum worthwhile treatment effect for this trial has been defined as 20 minutes. This is based on preliminary retrospective data (n=15) collected by the principal investigator after taking into account the time bowel care typically takes (i.e., 41 minutes). Therefore, a sample of 24 participants is required for an 80% power to demonstrate statistical significance on the primary outcome (time to complete bowel care) with an α level of 0.05 and with a worst-case dropout rate of 5%. This assumes a standard deviation (SD) of 18 minutes and a correlation of 0.04 to pre-post (before adjustment for the within-subject design). The estimated SD was derived from preliminary data collected as above (non-published data) and from the post data reported in the trial conducted by Christensen et al (27).

11.2 Population to be analysed

The trial will concentrate on adults living in the community who have a chronic spinal cord injury and persisting neurogenic bowel dysfunction.

11.3 Statistical Analysis Plan

All statistical analyses will be done using the principles of ‘intention to treat’. Regression models will be used to determine between group differences (and 95% CI). Results will be interpreted with respect to the pre-defined treatment effect of 20 minutes (39, 40) The ‘centile’ routine in Stata (v9.2; Statacorp, TX, USA) may also be used to derive the 95% CIs for median between group differences for data which is not normally distributed. This method does not make assumptions about the distribution of the data.

11.4 Interim Analyses

There will be no interim analysis of the data.

12 DATA MANAGEMENT

Data management will abide by the Research Data Management Policy of the University of Sydney (41) and all aspects will be outlined in a Research Data Management Plan.

12.1 Data Collection

All demographic data will be collected in paper format by the Associate Investigators (AI). Outcome data will be collected in paper format by the Blinded Assessors (BA).

12.2 Data Transfer

Once data have been collected, the AI / BA will scan the case report forms (CRFs) and upload it into Cloudstor. Cloudstor is a web based highly secured platform for transferring documents and is the supported method for data transfer by the University of Sydney (42). The AI / BA will not be able to see any other documents in the cloud. Only the Co-ordinating Principal Investigator and the Site Principal Investigator will be able to see all the documents that have been uploaded. This allows the safe transfer of data from the participants' homes (where the data will be collected) to the university. Once files have been downloaded by the Site Principal Investigator, they will be permanently deleted from Cloudstor. At the completion of the trial, any trial related paperwork (eg. Consent forms, participant information etc) will be transferred by the AI's using this same method to the University.

12.3 Data Storage

Once the data has been uploaded onto Cloudstor, the Site Principal Investigator will download the files and save them onto the University's Research Data Store (RDS) dedicated to this trial. The data from these files will also be transcribed into the University of Sydney's approved Data storage system (RedCap) by the Site Principal Investigator as per policy and procedure (41, 42). Access to data will only be granted to the Principal Investigators and other research staff directly involved in the study. At the end of the data collection process, the project status of RedCap will be changed to data analysis/clean up to ensure no further changes can be made to the data.

At completion of the trial the full dataset, codebook and data dictionary will be exported from RedCap and saved in the RDS.

All original paper copies of CRFs will be destroyed using a confidential shredder by the AI/BA in the community once they have been electronically stored on RedCap and the RDS.

12.4 Data Confidentiality

All information collected for this trial will be re-identifiable. This is necessary for accurate data entry and communication with the participants. Case Report Forms will include the initials, study number and date of birth of the participant. As per previous, consent forms and all files containing participants' personal details will remain in the Principle Site Investigator's locked office. Individual names of the participants will not be considered in data analysis and they will not be identified in published data. Any data stored for future analysis will be de-identified.

Computer software and servers that are approved by the University for either the level of encryption or security will be used to ensure that confidentiality of the data is maintained.

All hard copies of the CRFs will be destroyed using a paper shredder and confidential waste bin to ensure that no information can be identified. The results of the study will be published in peer reviewed journals. Results may also be presented at national and international conferences or

similar. Individual participants will not be identifiable in any publications or presentations. Participants may be able to request their own results from the Co-ordinating / Site Principal Investigator. The study will form part of a student thesis for a Doctor of Philosophy offered by the University of Sydney.

12.5 Study Record Retention

All source documents and trial documentation uploaded into the RDS and Redcap will be stored for 15 years.

13 ADMINISTRATIVE ASPECTS

The trial will be registered at the Australian and New Zealand Clinical Trial Registry prior to randomisation of the first participant. It has a universal trial number (UTN): U1111-1259-9022.

13.2 Independent HREC approval

This study has been approved by the Northern Sydney Local Health District HREC, reference number 2020/ETH02994.

13.3 Amendments to the protocol

Any amendments will be submitted to the HREC for review prior to implementation as per HREC guidelines.

13.4 Protocol deviations

Any protocol deviations will be submitted to the HREC for review.

13.5 Participant reimbursement

Participants will not receive any financial reimbursements.

13.6 Financial disclosure and conflicts of interest

This trial does not have commercial sponsorship and is an investigator-driven clinical trial. There are no conflicts of interests.

14 USE OF DATA AND PUBLICATIONS POLICY

One key publication of the primary results will be written. The first author will be Louise Kelly. Authorship will be determined by everyone involved. All clinicians involved in the trial will be acknowledged. In addition, all authors will need to comply with the International Committee of Medical Journal Editors' (ICMJE) policy on authorship. All data will be stored centrally at the University of Sydney. Sites will not use data collected for this trial for other purposes or publications without written permission.

As per ICMJE, individual participant data (IPD) and related dictionaries for all primary and secondary outcomes will be made available as a supplementary file to anyone for any type of analyses at the time of publication with no end date.

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