STUDY PROTOCOL

Pilot Study of SuperSeton Placement in Patients with Perianal Fistulas

The SuperSeton Feasibility Study

PROTOCOL TITLE:

Feasibility Study of SuperSeton Placement in Patients with Perianal Fistulas

Short title	The SuperSeton Feasibility Study
Acronym	The SuperSeton Feasibility Study
Version	4
Date	16-05-2017
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PROTOCOL SIGNATURE SHEET

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form (General Assessment and Registration form) is the application form that is required for submission to the accredited Ethics Committee (ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials GCP Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
(S)AE	**Serious Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinformatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Perianal fistulas are a common incapacitating problem. Many patients are treated by seton drainage to prevent recurrent abscess formation. Nowadays, vessel loops or sutures are used for drainage. The knot of these seton drains can cause complaints of pain or tenderness if it presses against the external opening of the fistula or even slides in to the fistula tract. Medishield B.V. designed a knotless seton drain, the SuperSeton. This could decrease the pain complaints caused by the knot.

Objective: With this study we aim to determine the feasibility of SuperSeton placement in patients with perianal fistulas.

Study design: The design of the study is a feasibility study.

Study population: Patients (≥ 18 years) with perianal fistulas (ever) treated with a knotted seton are eligible.

Intervention: The SuperSeton will be placed at the outpatient clinic in patients that already have a seton in situ. This seton will then be exchanged by the SuperSeton. In case patients do not have a seton in situ, the SuperSeton can be placed at the operating theatre in day care setting instead of a regular seton.

Main study parameters/endpoints: The primary outcome is seton failure (loosening of the seton). Secondary outcomes are time of procedure, complications and quality of life measured by the PDAI ('Perianal Disease Activity Index').

Nature and extent of the burden and risks associated with participation: The SuperSeton will be placed in patients with perianal fistulas (ever) treated with a conventional knotted seton. There are no additional risks involved. The seton will be placed at the outpatient clinic in patients with a seton in situ, or at the operating theatre in day care setting in patients with a perianal abscess without a seton. The material that is used for the Setons is of medical grade polyurethane, this is the same material of catheters that are already used in clinical practice (instech BTPU 027). The Setons including the insert (BTPU) are supplied sterile (Synergy Health). **Sample size calculation:** A group of 60 patients will be included to determine feasibility of the SuperSeton. The proposed treatment protocol is considered feasible if at least 70% of the SuperSetons stay in place.

PARTICIPATING CENTRES

	Surgeon
Academic Medical Center	Prof. dr. W.A. Bemelman Dr. C.J Buskens
Proctos Kliniek	Drs. C.B.H. Molenaar

INTRODUCTION AND RATIONALE

1.1 Introduction & rationale

Perianal fistulising disease is associated with local pain, discharge, and considerable morbidity rates (including sphincter and perineal tissue destruction) resulting in a negative impact on quality of life.[1] The main cause of perianal fistula development is sepsis originating from the cryptoglandular glands.[2] Other aetiologies are Crohn's disease (CD), malignancies, radiation, trauma or foreign bodies. In simple or low fistulas (lower one-third of the external sphincter) treatment consists of lay open techniques and recurrences are hardly seen.

In contrast, complex or high perianal fistulas (upper two-third of the external sphincter) have limited treatment options. The most frequently used treatment approach has been surgical non-cutting seton placement for chronic drainage of the fistula. This technique dates back to the ancient times. A seton maintains patency of the tract and eliminates the accumulation of pus which prevents the recurrent formation of tracts and abscesses. In addition, fibrosis of the fistula tract can be achieved.

However, the seton has been reported to negatively influence quality of life and is associated with a decreased Perianal Disease Activity Index (PDAI score).[3] Closure rates after seton removal vary widely in patients with CD (13.6%-100%).[4] Nowadays, vessel loops or sutures are used as seton to drain the fistula. The ends of the seton drain are connected by a knot or a suture according to known methods. A knotted seton is relatively difficult to clean, and the knot has a tendency to rotate towards the external opening of the fistula tract and sometimes even migrate in to the fistula tract. This may cause complaints of pain and discomfort. This matter is widely discussed on patient forums. Last year, a survey regarding complaints of the knot of the seton, was send via the website of the CCUVN (Crohn en Colitis Ulcerosa Vereniging Nederland) to patients with perianal fistulas. This survey showed that complaints varied from irritation, discharge of blood and/or pus, pain and itching. Sitting and bicycling were mentioned as activities that aggravated the symptoms. Up till now one other knotless seton is available, the Comfort Drain.[5]

Recently, MediShield B.V. developed a knotless seton, the 'SuperSeton'. This seton connects the two ends of the drain to form a smooth closed loop. It is expected that this smooth joint will decrease pain and discomfort in patients with perianal fistulas that are treated by seton drainage. In addition, the SuperSeton can make placement of the seton less complex for the surgeon.

With this study we will be able to comment on the feasibility of the SuperSeton.

2. OBJECTIVES

With this study we aim to determine the feasibility of SuperSeton placement in patients with perianal fistulas.

Primary Objective:

The primary objective of this study is to determine feasibility of the SuperSeton drain.

Secondary Objectives:

Secondary outcomes are time of procedure, complications and quality of life measured by the PDAI ('Perianal Disease Activity Index').

3. STUDY DESIGN

The design of the study is a feasibility study with SuperSeton placement in patients with perianal fistulas. The trial will be conducted in the AMC and the Proctos Kliniek. Patients fulfilling the inclusion criteria without any exclusion criteria will be included in the study. The total inclusion is scheduled to take place within 10 months.

Patients will be seen at the outpatient clinic 3 months after SuperSeton placement by the surgeon. Other visits will be scheduled on indication. During these contacts the PDAI score will be assessed. Patients will be followed by the research resident to assess complications or re-admissions.

4. STUDY POPULATION

4.1 Population (base)

Patients with a perianal fistula for which a seton was already placed in day care setting (that is still in situ) and patients presenting with a recurrent perianal fistula (ever treated with a knotted seton) for which a new seton will be placed are eligible.

4.2 Inclusion criteria

- ≥ 18 years
- Written informed consent
- Perianal fistula with a seton in situ or a recurrent perianal fistula for which a new seton will be placed

4.3 Exclusion criteria

- Patients with a pacemaker or an ICD in situ
- Rectovaginal fistula
- Patients with a stoma
- Life expectancy < 2 years
- The inability of reading/understanding and filling in the questionnaires
- Dementia or altered mental status that would prohibit the understanding and giving of informed consent
- Participation in another trial

4.4 Sample size calculation

The sample size calculation is based on a clinically relevant decrease in the PDAI and number of re-interventions. The PDAI has 5 items, subdivided in a 5-point Likert scale (range 0-20). A score of >7 is considered as serious perianal disease. The CCUVN survey indicated that the PDAI reflected severe complaints in Crohn's fistula patients, with high scores on all 5 scales (average 9.2). A decrease to 6.9 is considered to be clinically relevant (<7 considered as moderate perianal complaints). In the survey it also became apparent that 50% required re-interventions related to the knot. Reducing the 50% of reinterventions to 30% is considered clinically important and can be expected due to the stronger insert connection and less knot-related complaints.

The sample size needed to demonstrate superiority of the SuperSeton with a significant decrease in PDAI and number of re-interventions is 60 patients (alpha 0.05, power 90%, and 5% drop-out).

Feasibility:

The proposed treatment protocol is considered feasible if at least 70% of the SuperSetons stay in place.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Patients with an established perianal fistula and a seton in situ or for which a new seton will be placed will be included in the study.

All patients start with the placement of the SuperSeton at the outpatient clinic or at the operating theatre in day care setting. The flow chart is demonstrated in the attached figure 1 (Appendix). After 3 months, the feasibility of the SuperSeton will be assessed.

The SuperSeton is made of medical grade Polyurethaan, which is widely already used in clinical practice as catheters (instech BTPU 027). The setons including the insert (BTPU) are delivered sterile (Synergy Health).Therefore, there is no additional risk associated with SuperSeton placement.

6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint

- The primary outcome is seton failure (loosening of the seton)

6.1.2 Secondary study parameters/endpoints (if applicable)

- Procedure time
- Complications
- Disease activity and quality of life, as measured with the Perianal Disease Activity Index (PDAI) score

6.2 Study procedures

Informed consent will be obtained at the outpatient department in all eligible patients by the study team. Seton replacement will be performed at the outpatient clinic and new setons will be placed at the operating theatre in day care setting. All patients will be followed for 3 months by the study team. The flow chart is provided in the attached figure 1 (Appendix).

Patients will be contacted by telephone after ± 3 months the study coordinator to assess complications, additional interventions, re-admissions, duration of hospital stay and visits to the outpatient clinic.

6.3 Questionnaires

The following questionnaire will be used:

PDAI score: The Perianal Disease Activity Index (PDAI) is the gold standard for evaluating the severity of perianal disease. It includes five items: discharge, pain, restriction of sexual activity, type of perianal disease, and degree of induration. Each category is graded on a 5-point Likert scale ranging from no symptoms to severe symptoms.

6.4 Withdrawal of individual subjects

Patients can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

SAFETY REPORTING

6.5 Section 10 WMO event

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor

will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

6.6 Adverse and serious adverse events

Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational procedure. All adverse events reported spontaneously by the subject, or observed by the investigator or his staff will be recorded.

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation
- results in persistent or significant disability or incapacity;
- is a new event of the study likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

An *adverse reaction* (AR) is an untoward and unintended response to the investigational product(s) related to any dose administered.

A *suspected serious adverse reaction* (SSAR) is a serious adverse reaction, of which the nature, or severity, is consistent with the applicable product information i.e. the summary of the product characteristics.

A *suspected unexpected serious adverse reaction* (SUSAR) is a serious adverse reaction, of which the nature, or severity, is not consistent with the applicable product information i.e. the summary of the product characteristics.

Reporting procedure applies to all (S)AE's occurring from the time a subject gives consent until 30 days after the last study medication administration and to any SAE that occurs after the 30-day period, if it is considered to have a reasonable possibility to be related to the protocol treatment or study participation.

A life threatening SAE, or SAE with death as a result, must be reported within 7 days after the local investigator has been informed. Other SAEs must be reported within 15 days.

The study coordinator is responsible for reporting SAEs at CCMO module 'ToetsingOnline'. Using the CCMO module 'ToetsingOnline', all SAEs will be reported to the CCMO and central METC. By means of this website notifications will be sent to the relevant authorities (METC/LAREB/EudraVigilance). The reporting will occur within 15 days after the investigator has first received information on the SAE. For fatal or life-threatening cases a preliminary report will be offered within 7 days followed by a complete report within 8 days.

The following SAE's do not require immediate reporting but will be reported once yearly in line-listings to the accredited METC that approved the protocol:

- Elective hospitalization for pre-existing conditions that have not been exacerbated by trial treatment
- A hospitalization which was planned before the subject consented for study participation and where admission did not take longer than anticipated
- Social and/or convenience admission to a hospital
- Disease recurrence in the follow-up period requiring hospitalisation

6.6.1 Suspected unexpected serious adverse reactions (SUSAR)

SUSARs will be electronically reported via ToetsingOnline and the trial coordinator will communicate all SUSARs to the independent monitor and to the steering committee (WA Bemelman and CJ Buskens) of this study.

6.7 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and or referral to the general physician or a medical specialist.

6.8 Data and safety monitoring and Data Safety Monitoring Board (DSMB)

This study is considered a low risk trial. Therefore no DSMB will be installed. The AMC study coordinator will monitor the data.

Furthermore, to keep insights in SAE's, the trial coordinator will communicate all SAE's to the the steering committee (WA Bemelman and CJ Buskens) of this study. The steering committee will comment on the reports.

STATISTICAL ANALYSIS

6.9 Statistics

All data will be collected in an electronic database by the AMC study coordinator. The outcome parameters will be analysed after 3 months follow up with appropriate statistical tests using the statistical program SPSS. A two-tailed $p < 0.05$ is considered statistically significant. Descriptive statistics will be used to describe patient characteristics and outcomes. Preoperative PDAI scores will be compared to postoperative PDAI scores after 3 months follow up. Results will be analysed using the paired *t*-test.

7. ETHICAL CONSIDERATIONS

7.1 Regulation statement

This trial will be conducted according to the principles of the declaration of Fortalezea Brazil (October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other European guidelines, regulations and acts. Data management, monitoring and reporting of the study will be carried out in accordance with the ICH GCP guidelines.

7.2 Recruitment and consent

The information offered to the patient or representative contains:

- A statement that the trial involves research
- A full and fair explanation of the procedures to be followed
- A full explanation of the nature, expected duration, and purpose of the study
- A description of any reasonable foreseeable risks or discomfort to the patient
- A description of any benefits which may reasonably be expected
- A statement that patient data will be handled with care and confidentiality
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits, in which case the patient will receive standard treatment with the same degree of care

7.3 Objection by minors or incapacitated subjects (if applicable)

Minors and legally incompetent adults are excluded from the trial.

7.4 Compensation for injury

The AMC Medical Research BV has insurance, which is in accordance with the legal requirements in The Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of June 23, 2003). This insurance provides cover for damage to research subjects through injury or death caused by the trial:

- € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the research;
- € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the research;
- € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organization for all damage disclosed by scientific research for the AMC as ‘Sponsor (verrichter)’ in the meaning of said Act in each year of insurance coverage. The insurance applies to the damage that becomes apparent during the study or within 4 years after.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

7.5 Incentives (if applicable)

Enrolled patients will not receive any special incentives, compensation or treatment through participation in this trial, except for covering of travel expenses in case of additional appointments to standard care.

7.6 Handling and storage of data and documents

Every randomised patient will be assigned a three-digit study number. Communication occurs only with this number. The full name and birth date of the patient will only be recorded on the informed consent form.

A study coordinator coordinates the study, monitors patient inclusion and protocol steps, data collection, data entry, preparation and performs analyses and will report the data. Continuous data monitoring, and data collection on a CRF will guarantee complete and real-time prospective recording of data. All data (personal, medical and other relevant information) will be sent by the local investigators to the AMC. After study completion all data will be stored (15 years) at the AMC in a separate, closed room.

7.7 Monitoring

The study will be monitored by the AMC study coordinator

7.8 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion. All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

7.9 Annual safety report

The study coordinator will submit a safety report after completion of the trial to the accredited METC. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the study, serious adverse events/ serious adverse reactions, other problems, and amendments.

7.10 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit. In case the study is ended prematurely, the investigator will notify the accredited METC, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

7.11 Public disclosure and publication policy

Patients are entitled to public disclosure of the results of the trial on the basis of their participation in it. The results of research will be submitted for publication to peer-reviewed scientific journals. Agreements with respect to participation in publication will be made before the start of the trial.

8. TIME SCHEDULE

July 2016:

Obtaining Ethic Committee Approval AMC

Second half of 2016 until June 2017:

Start clinical study

Inclusion of patients

Follow up of included patients

Data management

Analysis of data

Writing report

9. REFERENCES

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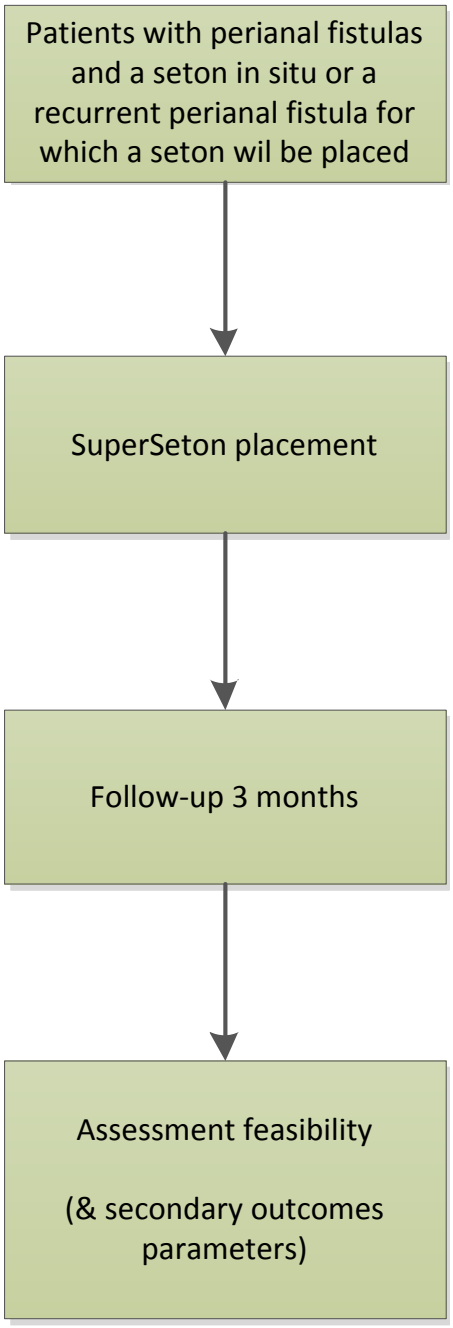
5. Riss S. B-HT, Stift A. The Comfort Drain: a new device for treating complex anal fistula. Tech Coloproctol 2014;18:1133-5.

10. APPENDIX



Appendix. Figure 1: flow chart of trial design