

BMJ Open Inforatio technique to promote wound healing of diabetic foot ulcers: study protocol for a parallel-group, evaluator-blinded, randomised clinical trial

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ABSTRACT

Introduction Diabetic foot ulcers (DFUs) are associated with extensive consequences for the affected patients and treatment of these hard-to-heal ulcers is known for being challenging. New treatment methods to supplement the current standard care may improve the prognosis for these patients.

A preceding feasibility trial with promising results, facilitated this trial that aims to study the effect of a novel simple treatment, called inforatio technique, which may promote healing of DFUs. The inforatio technique is a minimally invasive procedure where small cuts are made on wound beds with punch biopsy tools.

Methods and analysis This multicentre randomised clinical trial will be conducted at outpatient clinics at Zealand University Hospital, Herlev University Hospital, Slagelse Hospital and Nykøbing Falster Hospital. 100 participants will be included and randomised in a 1:1 ratio to either a control group that receives usual care or an intervention group that receives both usual care and the inforatio technique.

The primary outcome is complete healing evaluated on digital images by blinded observers. It is not possible to blind participants or the outpatient clinic staff because the inforatio technique is visible in wound beds after application. Change in EQ-5D-5L (EuroQoL-5 Dimension-5 Level) Visual Analogue Scale Score and Wound-QoL Global Score from baseline to end of follow-up are secondary outcomes.

Ethics and dissemination Ethics approval has been granted by the Danish National Committee on Health Research Ethics on 15 December 2021 (approval ID: SJ-904). Trial results are planned to be published in a high-impact peer-reviewed journal.

Trial registration number NCT05189470.

INTRODUCTION

Chronic foot ulcers affect the quality of life of people with diabetes widely and is associated with increased mortality and morbidity.^{1–5} Of people with diabetes 15%–25% develop chronic foot ulcers during their lifetime, 50%–60% of diabetic foot ulcers (DFUs)

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The trial will provide evidence on the effect of a novel, simple, minimally invasive and low-cost treatment that may benefit people with diabetes worldwide.
- ⇒ A strength of the study is that it is based on a feasibility trial that showed promising results for healing when the inforatio technique was applied. Patient acceptability was high and no intervention-related adverse event was found.
- ⇒ Other strengths of the study include the following; it is a multicentre trial, the treatment is evaluated in a usual clinical setting, patients will be randomised, and external validity will be high due to the pragmatic design.
- ⇒ Limitations of the study include; the population is expected to be heterogeneous, and the usual care may differ minimally between centres, which is addressed by stratifying randomisation for centre and by adjusting for several clinically relevant factors in the primary analysis of healing.

become infected and 20% of patients with infected DFUs undergo lower extremity amputations.^{2 3 6} The treatment of these hard-to-heal ulcers is challenging. Around 70% of non-infected DFUs will not heal within 20 weeks when treated by standard wound care principles,⁷ and only 45% of patients will become both ulcer-free without amputation and alive 12 months after the onset of a DFU.⁸ Development of new treatment methods that can supplement today's standard care is necessary to improve the prognosis for patients with DFUs. For this purpose, more randomised clinical trials that assess the effects of new DFU treatments must be conducted.^{9 10}

The inforatio technique is a novel, minimally invasive procedure where small cuts are made on wound beds with punch biopsy tools

without involving wound edge epithelia. The treatment is applied after the wound has been surgically debrided for slough and devitalised tissue. The aim is to cause controlled bleeding and initiate an acute inflammatory response that promotes healing.

The inforatio technique was developed by our research group after an unexpected qualitative observation when punch biopsies were taken from DFUs for basic research purposes. Formation of granulation tissue and epithelialisation appeared to enhance at spots in the wound bed where biopsies were taken. These observations facilitated a feasibility trial that showed promising results; 6 of 10 patients had complete healing of their DFU within 20 weeks after treatment when the inforatio technique was commenced.¹¹ No harmful intervention-related effects were found in the feasibility trial. To our knowledge, there are no studies in the literature about methods similar to the inforatio technique apart from the above-mentioned feasibility trial.¹¹

This randomised clinical trial aims to assess whether the proportion of ulcers that heal within 20 weeks is higher when DFUs are treated with the inforatio technique in addition to usual wound care compared with treatment with usual wound care alone. The inforatio technique has a global potential for treatment of an increasing number of patients with DFUs if the treatment is shown to promote healing.

METHODS

Trial design

This multicentre trial is a two-armed, parallel-group randomised clinical trial with blinded evaluation.

Trial setting and participants

The recruitment and follow-up will be conducted at the wound care outpatient clinics of Zealand University Hospital, Herlev University Hospital, Slagelse Hospital and Nykoebing Falster Hospital by a multidisciplinary staff consisting of wound care nurses, podiatrists and orthopaedic surgeons. The staff will screen patients at the respective outpatient clinics according to the following eligibility criteria:

Inclusion criteria

- ▶ Age ≥ 18 years.
- ▶ Diabetes mellitus.
- ▶ Non-surgical ulcers located distal to the malleoli.
- ▶ An ulcer diameter of ≥ 4 mm.
- ▶ A patient-reported wound duration of ≥ 6 weeks.

Only one ulcer will be included from each participant. If a patient has more than one eligible ulcer, the largest ulcer will be included. In case of equally sized ulcers, the ulcer with the most recent onset will be included.

General exclusion criteria

- ▶ Dementia or other reasons for inability to give informed consent.

- ▶ Malignant disease.
- ▶ Current treatment with systemic immunosuppressive drugs.

Exclusion criteria related to the index extremity

- ▶ Surgeons have either diagnosed the patient with or suspect that the patient has; acute phase neuroarthropathy or osteomyelitis underlying the index ulcer.
- ▶ Neither the dorsalis pedis arterial pulse nor the posterior tibial arterial pulse are palpable and the systolic toe pressure is < 30 mm Hg (measured within the last 6 months).
- ▶ The index foot is amputated at mid-foot level or proximal to mid-foot level.
- ▶ The patient awaits or has undergone a revascularisation procedure within the last 8 weeks.
- ▶ Gangrene.

Exclusion criteria related to the index ulcer

- ▶ An infection of the index ulcer defined by the International Working Group on the Diabetic Foot/Infectious Diseases Society of America system classification as presence of at least two of the following; (1) Local swelling or induration; (2) Erythema > 0.5 cm to ≤ 2 cm around the ulcer; (3) Local tenderness or pain; (4) Local warmth; or (5) Purulent discharge.¹²
- ▶ An ongoing antibiotic treatment due to an infection of the index ulcer.
- ▶ Positive probe-to-bone test.
- ▶ Exposed joint or tendon.
- ▶ The soft tissue layer of the wound bed is too thin to allow application of the inforatio technique without exposing bone or tendon.
- ▶ Interdigital ulcer location.

Interventions

All participants will receive the usual care of the respective outpatient clinics. The usual care includes offloading treatment; debridement of slough and devitalised tissue in wound beds; debridement of callosities; and application of dressings that maintain a moist wound environment.

Participants that are randomised to the intervention group will receive the inforatio technique at baseline, 3 weeks, 6 weeks, 9 weeks and 12 weeks as long as the ulcer has a diameter of minimum 4 mm because the treatment cannot be applied to smaller ulcers without involving epithelia.

The inforatio technique is a minimally invasive treatment where small cuts are made with 2 mm, sterile punch biopsy tools in the periphery of wound beds after the ulcers have been debrided (see [figure 1](#) and [figure 2](#)). The treatment does not involve wound edge epithelia. The depth of the cuts will depend on the underlying anatomy and will be a maximum of 3.5 mm, which is half the length of the punch biopsy tool steel bands. The application pattern will be similar to the definition from the feasibility trial;¹¹ approximately 2 mm from wound edges, and 5 mm between the cuts. Application is avoided



Figure 1 A diabetic foot ulcer before (left) and after (right) inforatio technique has been applied.

on spots in the wound bed where the soft tissue layer is too thin to allow a cut without reaching bone or joint. The procedure is applied by orthopaedic surgeons from the recruiting centres.

Application of the inforatio technique will be discontinued for the remaining period of follow-up if participants develop an infection in the index ulcer; necrosis in the wound bed; a positive probe-to-bone test; exposure of joint or tendon; an unexpected intervention-related harmful event or are diagnosed with underlying osteomyelitis.



Figure 2 The 2 mm punch biopsy tool that is used for application of the inforatio technique.

Trial schedule

Table 1 gives an overview of the trial enrolment, interventions and assessments according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines.

The recruitment will be depicted in a CONSORT (Consolidated Standards of Reporting Trials) flow diagram (**figure 3**). The baseline trial visits will be conducted on the day when randomisation has been performed by one of the investigators. There are six follow-up visits during a clinical follow-up of 20 weeks (**table 1**). If the index ulcers are not seen by a nurse or a medical doctor within 1 week from baseline, a safety visit will be conducted 1 week from baseline to ensure a close clinical control at the beginning of the trial participation.

The mid-trial visits are missed if the following cannot be fulfilled: (1) The visit is within a window of ± 7 days; and (2) The visit is minimum 2 weeks after the previous trial visit. The window for the 20-week visit is from 20 weeks to 22 weeks and 4 days after baseline. If participants are hospitalised at the recruiting centres during their follow-up, the staff from the outpatient clinic will conduct the trial visits at the department of hospitalisation if participants consent to it.

Follow-up ends whenever one of the following appears; healing (observed by the staff at the outpatient clinic); the 20-week visit; an amputation at any level of the index limb; or death. Digital images of ulcers are taken at baseline and at the last trial visit after debridement and before application of the inforatio technique with an angle of approximately 90° on the wound bed. Rulers are placed next to the ulcers as size references. If an ulcer has healed during follow-up, an image is taken with a ruler located near the original location of the ulcer to ensure evaluator blinding.

The participants are lost to follow-up if they withdraw their consent to participate or move out of their baseline habitation to an address that is located outside the two Danish regions in which the centres are located.

In addition to the clinical follow-up, a 1 year follow-up will be conducted on amputation and death based on information from medical journals.

Outcomes

Primary outcome

The primary outcome is healing assessed separately by two blinded observers on digital images taken at the last trial visits. The observers will discuss any disagreements until agreement is reached. Healing is defined as complete epithelialisation without any discharge from the site of the index ulcer. Any discrepancy between the blinded assessment of healing on images and the unblinded clinical assessment at trial visits, will be reported. Another randomised clinical trial about healing of DFUs used the same approach on assessment of healing and reported cases with discrepancies between clinical assessment and assessment of healing on images.¹³ Some cases were due to poor quality of the images and other images were

Table 1 The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) table

	Study period									
	Enrolment	Allocation	Postallocation							Close-out
WEEK		o	1*	3	6	9	12	16	20	52
ENROLMENT										
Eligibility screen	x									
Informed consent	x									
Allocation		x								
INTERVENTIONS:										
Inforatio technique (for the intervention group)†	x		x	x	x	x				
Usual care	x		x	x	x	x	x	x	x	
ASSESSMENTS										
Blood samples (HbA1c** and eGFR¶)	x									
10 mg monofilament assessment of the index foot‡	x									
EQ-5D-5L and Wound-QoL††	x								x§	
Ulcer digital image	x								x§	
Wound area measurement on digital images	x								x§	
Clinical assessment of healing (unblinded)			x	x	x	x	x	x	x	
Blinded assessment of healing on digital images									x§	
Documentation of adverse events			x	x	x	x	x	x	x	
1-year amputation and death										x

*The 1 week visit is a safety visit that is only conducted for participants who otherwise do not receive treatment of their index ulcers by nurses or medical doctors within 1 week from baseline.

†Participants in the intervention group receive the inforatio technique treatment as long as their index ulcer has a diameter >4 mm and does not develop infection, necrosis, positive probe-to-bone test, exposure of joint or tendon; or underlying osteomyelitis.

‡This test is conducted if the participant has not previously been diagnosed with peripheral neuropathy. The assessment is conducted according to the International Working Group on the Diabetic Foot guidelines.²⁰

§These assessments are conducted at the last trial visit, which may be before 20 weeks from baseline if healing is reached sooner.

¶Estimated Glomerular Filtration Rate)

**Hemoglobin A1c

††The EuroQoL-5 Dimension-5 Level questionnaire and the Wound-Quality of Life questionnaire.

reported as not being able to confirm healing observed in the clinical setting. Remaining scar tissue after healing may be a reason why healing observed in the clinic cannot be confirmed on images.

The primary outcome is registered as non-healing in case of death and amputation.

Secondary outcomes

The Visual Analogue Scale (EQ VAS) from the EQ-5D-5L (EuroQoL-5 Dimension-5 Level) Questionnaire and the global score from the Wound-QoL (Wound Questionnaire) are used to assess change in general health status and disease-specific quality of life from baseline to end of follow-up.

The participants complete the Danish versions of the EQ-5D-5L and the Wound-QoL unsupervised in a waiting room at the day of their baseline and last trial visit. The questionnaires will be screened by a staff member for

incomplete item responses when participants deliver the questionnaires.

The EQ-5D-5L is a general health patient-reported outcome measure (PROM) from which the EQ VAS measures self-rated health. The EQ VAS ranges from 0 to 100 with 0 representing 'The worst health you can imagine' and 100 representing 'The best health you can imagine'.¹⁴

The Wound-QoL is a disease-specific PROM that consists of 17 items, each of which has a score from 0 to 4. Zero indicates no problem and 4 is the highest score for an ulcer-related problem. The global Wound-QoL Score is the average of all item scores.^{15 16}

If participants die during the clinical follow-up, the Wound-QoL Global Score and the EQ VAS Score will be registered as missing. If the index extremity undergoes amputation, participants are asked to complete the EQ-5D-5L 20 weeks after the amputation has been

CONSORT 2010 Flow Diagram

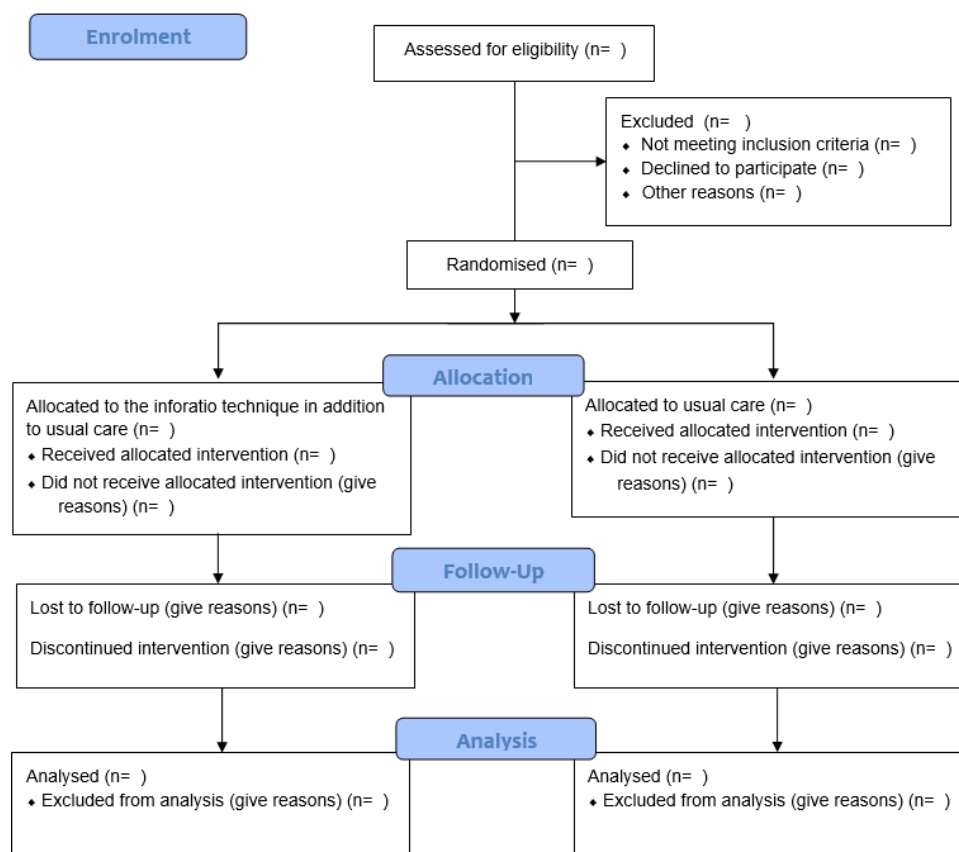


Figure 3 The CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

performed and the Wound-QoL Global Score will be registered as 4.

The Wound-QoL response is defined as missing if less than 13 of the 17 items have been completed.¹⁵ Participants that forget to complete the questionnaires at their last trial visit; fill out the questionnaires incorrectly; or are lost to follow-up are offered to complete the questionnaires at their next non-trial visit at the outpatient clinic or to complete the questionnaires by letter.

Permission to use the EQ-5D-5L (registration ID 39403) and the Wound-QoL has been granted.

Safety outcome

Safety will be assessed based on observed and patient-reported adverse events and the relatedness of the events to the index ulcer (table 2). Relatedness of adverse events to the inforatio technique will be qualitatively assessed based on the following categories: (1) Definitely related (the event can be fully explained by the intervention); (2) Probably related (the event is most likely to be explained by the intervention rather than other treatments or the clinical condition of the participant); (3) Probably not related (the event is most likely to be explained by other treatments, an expected natural course of DFUs or the clinical condition of the participant); and (4) Definitely

not related. Adverse events related to the inforatio technique are not expected, which is supported by the results from the feasibility trial.¹¹

Infection; enlargement of ulcers; and exposure of bone, joint and tendon are part of the natural courses of many DFUs and may necessitate hospitalisation, surgery or even amputation.^{2,3,6}

Sample size

A healing rate of 30.9% (95% CI 26.6 to 35.1) in 20 weeks has previously been reported in a systematic review that included non-infected DFUs treated by standard wound care principles.⁷ To our knowledge, there are no other systematic reviews that assess healing rates for DFUs receiving standard treatment. The feasibility trial that preceded this trial suggested that 60% of ulcers will heal during a follow-up of 20 weeks when patients receive the inforatio technique.¹¹

A power calculation with the power set at 80% and the α level at 5% gives a sample size of 84 participants for comparing a control group where 30% is expected to heal with an intervention group for which we aim to show that 60% will heal. To allow an attrition of 20%, the aim is to recruit 100 participants.

Table 2 Registration of adverse events

Adverse events related to the index ulcer	Patient-reported adverse events	Other adverse events
<ul style="list-style-type: none"> ▶ A total wound area increase during follow-up* ▶ Infection of the ulcer ▶ Exposure of bone, tendon or joint in the wound bed ▶ Osteomyelitis of the underlying bone is diagnosed ▶ A surgical wound intervention is performed in an operating theatre ▶ Hospitalisation related to the index ulcer ▶ Minor amputation of the index extremity (below ankle) ▶ Major amputation of the index extremity (above ankle) ▶ Mortality related to the ulcer 	<ul style="list-style-type: none"> ▶ Participants are asked at each trial visit whether they have experienced a recent onset of events that is related to their index ulcer and whether they suspect relatedness of these events to the trial interventions. ▶ Participants from the intervention group are asked whether they experience any adverse events during or after application of the inforatio technique 	<ul style="list-style-type: none"> ▶ All-cause mortality ▶ All-cause hospitalisation
<p>*A blinded assessor will estimate wound area on images from the baseline and last trial visits by performing digital planimetry with ImageJ software.²¹</p>		

Statistical analysis plan

Baseline characteristics will be reported with appropriate descriptive statistics. Differences in demographics and ulcer characteristics between allocation groups will be compared by conducting the appropriate statistics (χ^2 test for categorical variables and Student's t-test or Mann-Whitney U test for continuous variables depending on the nature of the data). The analyses of primary and secondary outcomes will be performed on the intention-to-treat population with participants being analysed as randomised regardless of the treatment received. Supplementary analyses will be performed on the per-protocol population, which excludes participants with one or more serious protocol violations as defined below:

- ▶ Participants not receiving their allocated treatment.
- ▶ Participants with inadequate adherence:
 - Participants that miss more than 50% of the follow-up visits.
 - Participants in the intervention group that miss more than 50% of the follow-up visits where the inforatio is supposed to be applied (the 3-week, 6-week, 9-week and 12-week visits).

The primary analysis of the trial will be a mixed effects logistic regression for healing within 20 weeks with centre of recruitment as a random effect and the following factors as fixed effects; baseline ulcer duration, baseline ulcer area, ulcer location (plantar/not plantar), baseline HbA1c (Hemoglobin A1c), and presence of four or more of the following diagnoses; hypertension, previous myocardial infarction, previous apoplexy, congestive heart failure, chronic obstructive pulmonary disease, liver cirrhosis, eGFR (estimated Glomerular Filtration Rate) <60 mL/min 1.73 m² and diabetic retinopathy. In case of discrepancy between blinded assessment of healing on images and unblinded clinical assessment

at trial visits, a sensitivity analysis will be performed for healing assessed clinically at trial visits. Time to healing will be reported descriptively and a Student's t-test will be conducted to compare time to healing between groups.

The EQ-5D-5L and Wound-QoL data will be presented descriptively in line with the guidelines for the questionnaires.^{14 15 17} A multivariate linear regression that adjusts for baseline score will be performed for the analysis of changes in the EQ VAS Score and the Wound-QoL Global Score from baseline to end of follow-up.

The safety outcome will be descriptively reported and analysed on 'as treated' basis where participants are grouped according to whether they received the inforatio technique. A statistical comparison between groups will be conducted by χ^2 tests and with estimates of relative risks for participants that experience; (1) Ulcer-related adverse events and (2) Serious adverse events (amputation of the index limb, all-cause mortality and ulcer-related hospitalisation) during follow-up. Unexpected inforatio-related adverse events will be descriptively reported.

An interim analysis of the primary, secondary and safety outcomes will be performed and published for the initial 50 patients that are recruited if recruitment cannot be completed. Significance is set at two-tailed values of $p < 0.05$. Underlying statistical assumptions for linear and logistic regressions will be assessed graphically.

Handling of missing data

Wound-QoL Global Scores and EQ VAS Scores that are missing due to death during follow-up will not be considered in the handling of missing data. Otherwise, missing data on the primary and secondary outcomes will be handled according to recommendations by Jakobsen *et al.*¹⁸ If the proportion of missing data is <5% for an outcome, the analysis of the outcome will be a

complete-case analysis. If more than 5% of the data are missing for an outcome, the analysis of the outcome will include missing data imputed by multiple imputation technique and a complete case analysis will be performed as a sensitivity analysis. In both cases, a best-worst and worst-best case sensitivity analysis will be conducted for missing data on healing.¹⁸

The imputation model for healing within 20 weeks, the final Wound-QoL Global Score and the final EQ VAS Score will include following auxiliary variables; centre of recruitment, baseline ulcer area, ulcer duration, ulcer location (plantar/not plantar), age, body mass index, smoking, alcohol consumption, baseline PROM Scores, baseline HbA1c, baseline eGFR, and amputation of the index limb during follow-up. Fifty sets of imputations will be conducted.

Randomisation and allocation concealment

In a 1:1 ratio, participants will be allocated to either the control group that receives the usual wound care of the outpatient clinics or the intervention group that receives both the usual wound care and the inforatio technique. The allocation is conducted by block randomisation with stratification by centre and will be generated with Research Electronic Data Capture (REDCap), which is a computerised irreversible randomisation application.¹⁹ Block sizes will be randomly alternating between two and four to prevent prediction of allocation assignment. Investigators will perform the randomisation by logging into the REDCap website and register the participants by civil register number. Adequate allocation concealment is ensured by the irreversibility of randomisation and the inability to predict the next allocation assignment in RedCap. The allocation will be revealed to the participant and wound care staff immediately after the randomisation has been conducted.

Blinding

The assessors of healing and wound area on digital ulcer images are blinded to the treatment allocations. The digital images will be blinded by the primary investigator before delivery to the assessors. Data analysts will also be blinded to the treatment allocation. It is not possible to blind participants or the staff that performs wound care and clinical assessment of healing because cuts are visible in the wound bed after application of the inforatio technique.

Patient and public involvement statement

The interview responses of participants from the feasibility trial have been taken into consideration in the process of designing the trial. Participants were asked about burden of participation, trial experience and suggestions for change in trial set-up.¹¹

Trial status

The first participant was included 10 March 2022 and 29 participants have been recruited so far (16 September 2022). Recruitment is expected to be completed 30 June

2023. The protocol for this randomised clinical trial follows the SPIRIT statement guidelines and is registered with the ClinicalTrials.gov ID NCT05189470, 12 January 2022.

Ethics and dissemination

Ethics approval has been granted by the Danish National Committee on Health Research Ethics, 15 December 2021 (approval ID: SJ-904). A data monitoring committee is not considered necessary as the trial is low-risk. Trial results are planned to be published in a peer-reviewed journal and authorships will follow ICMJE (The International Committee of Medical Journal Editors) recommendations. Protocol amendments will not be implemented before approval from the ethics committee has been obtained. Amendments will be registered on ClinicalTrials.gov and disseminated to participants. Insurance of the trial is covered by The Danish Patients Compensation Fund.

Data statement

Data management will be in compliance with The Danish General Data Protection Regulation and the Danish Data Protection Act. The data management plan has been approved by The Research Registry of Region Zealand, 10 January 2022 (ID: REG-116-2021). The full trial data set will be accessible to the primary investigator, sponsor and The Danish National Committee on Health Research for the purposes of management and audit of research development.

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Contributors The primary investigator SM led the process of designing and planning the trial; drafted and submitted the manuscript; prepared the statistical analysis plan supervised by statisticians at Odense University Hospital OPEN (Open Patient data Explorative Network) Statistics; contributed to the development of the inforatio technique; and is responsible for the overall coordination and conduct of the trial and management of the clinical data. HG has reviewed the draft versions of the manuscript; provided clinical expertise to the trial design and planning; contributed to the development of the inforatio technique; and is responsible for coordination and conduct of the trial at Herlev University Hospital. TSJ has reviewed the draft versions of the manuscript; provided clinical and scientific expertise to the trial design; and contributed to the development of the inforatio technique. TVA has reviewed the draft versions of the manuscript; and provided scientific expertise to the trial design. MRK has reviewed the draft versions of the manuscript; provided clinical expertise to the trial design and planning; and is responsible for the commencement of the trial at Nykoebing Falster Hospital. MRBL has reviewed the draft versions of the manuscript; provided clinical expertise to the trial design and planning; and is responsible for coordination and conduct of the trial at Zealand University Hospital. The trial sponsor SB has the overall responsibility for trial initiation and management; reviewed the draft versions of the manuscript; provided scientific and methodological oversight of the trial; contributed to the development of the inforatio technique; and has provided scientific expertise to the trial design and planning.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing is not applicable as no data sets were generated and/or analysed for this study. Data will be available upon reasonable request when the trial results have been published.

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