Statistical Analysis Plan

Sealed Therapeutic Shoe vs. Total Contact Cast as Treatment of Diabetic Foot Ulcers: a Multicenter RCT

Clinical Trial Registration Number: Unique Protocol ID: 18RS6667

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1   INTRODUCTION

1.1   STUDY BACKGROUND AND RATIONALE

Approximately 19-34 % of all people with diabetes will at some time in life develop a diabetic foot ulcer (DFU).[1] People with diabetes are especially prone to develop foot ulcers because of different diabetic complications, especially angiopathy and peripheral neuropathy.

The DFUs are often hard to heal and the treatment is long-lasting. The DFUs result in lower physical and mental quality of life and affects social relationships.[2] The treatment is also very costly,[1, 3] it has been estimated that 25-50 % of diabetic inpatient care is related to DFUs.[4] Despite extensive treatment, all DFUs do not heal but some end in amputation. People with diabetes are at a 25-fold risk of amputation and every 20 second a person somewhere in the world has the foot amputated because of diabetes.[5] 85 % of these amputations are preceded by a foot ulcer[6] and many of these ulcers and amputation could have been prevented.[7]

Total contact cast (TCC) as gold standard treatment of DFUs
Plantar DFUs often are the result of a combination of foot deformities that increase plantar pressures when the person walks and that the person keeps walking despite high pressure and ulcers because he or she has lost sensation in the feet because of sensory neuropathy. Literature reviews and international guidelines[8, 9] recommend non-removable knee-high offloading devices, for example, a total contact cast (TCC) to treat plantar DFUs, as this offloads the ulcer from mechanical loading all day and night. Still, TCC is not accepted by all patients and is contraindicated in a number of cases because of negative side-effects. Most of these side-effects are the consequences of immobilizing the ankle joint, which impairs gait and results in lower ambulatory activity. For example, side-effects include reduction of joint flexibility, weight gain, muscle atrophy, sick leave from work and social isolation.[10] In addition, a TCC can give secondary ulcers why weekly visits to the hospital is necessary to change casts. For these reasons, TCC is only used for a minority of the patients for whom it could be beneficial, despite being the gold standard treatment.[11]

For working patients, casting often means sick leave from work, but casting can also be difficult for older patients with impairments of gait and balance. For patients where TCC is contraindicated or not tolerated, guidelines recommend removable offloading devices despite it is well known that these devices are not very effective.[8] In practice, this means that many patients do not receive effective treatment. Another problem is that many patients get new foot ulcers after treatment with TCC,[12] in part because adherence to using therapeutic footwear after healing is lower than desirable.[13]

Sealed therapeutic shoe as alternative treatment
The investigators have developed a new treatment concept, sealed therapeutic shoe, which potentially can fill the need for effective ulcer treatment without limiting ambulatory activity with its associated negative consequences for physical, mental and social health, and to a lower cost, resulting in fewer obstacles for clinical use.

The concepts include therapeutic shoes with custom-made insoles, where the new part is how the insole is optimized to offload the ulcer from mechanical loading and that the shoe is "sealed" with a soft plastic strap and is used day and night, like a cast, and is only removed when changing the ulcer dressings. The ulcer is thereby offloaded but the person is free to ambulate and work as usual, and no cast changes are necessary. In addition to effective ulcer treatment and fewer side-effects the investigators hope that the

positive experience of that high adherence to using therapeutic shoes results in healing will lead to higher adherence after healing, and thereby reduction of the risk of ulcer recurrences in the future. The method to offload foot ulcers was first tested in a case-study, where the investigators found that the shoe and insole effectively offloaded the ulcer.[14] After this, the whole sealed shoe concept was evaluated in a feasibility study[15] on seven people with DFU. All ulcers healed and complications were few. The investigators are now going to evaluate the effects of sealed therapeutic shoes compared to gold standard treatment, that is, TCC.

1.2   HYPOTHESES AND OBJECTIVES

The overarching objective is to evaluate whether sealed shoe can heal DFU at least as effectively as TCC, but with fewer adverse events during the treatment period, better long-term effects and to a lower cost.

Specific objectives
Objective 1. To investigate whether a sealed shoe can heal DFUs at least as effectively as TCC (non-inferiority, one-sided hypothesis testing).
Objective 2. To investigate whether there is a difference in adverse events during the treatment period with sealed shoe and TCC (superiority, two-sided hypothesis testing).
Objective 3. To investigate whether there is a difference in long-term effects (up to 12 months after end of treatment) with sealed shoe and TCC (superiority, two-sided hypothesis testing).
Objective 4. To investigate whether there is a difference in health economic outcomes between treatment with sealed shoe and TCC (superiority, two-sided hypothesis testing).

The null hypotheses are that a sealed therapeutic shoe does not heal DFUs at effectively as TCC, and that there are no differences between sealed shoe and TCC in side-effects, long-term effects and health economic outcomes.

2   STUDY METHODS

2.1   OVERALL DESIGN

The study is a randomized controlled trial with two parallel groups (intervention group using sealed shoe and control group using TCC) and an allocation ratio of 1:1.

2.2   RANDOMIZATION

The randomization will be stratified for study site and ulcer area (smaller or bigger than 1 cm^2, ulcer size calculated as longest diameter*longest perpendicular diameter) and use random permuted blocks of randomly varying size. The randomization details are stored on a protected server of Region Örebro County and cannot be accessed by those who provide clinical input to the SAP.

2.3   SAMPLE SIZE

The sample size calculation was performed using http://powerandsamplesize.com/Calculators/ Compare-2-Proportions/2-Sample-Non-Inferiority-or-Superiority. Primary outcome is proportion of healed ulcers after 12 weeks of treatment. Based on the literature and our feasibility study the proportion of healed ulcers after 12 weeks treatment is estimated to 90% with sealed shoe or TCC.[15, 16] If accepting p=0.05, a statistical power of 80% and a non-inferiority limit of 10%, 112 participants are

needed. To compensate for attrition of participants during the long-term follow up of secondary outcomes, the aim is to recruit 150 participants. The participants will be randomized to treatment with sealed therapeutic shoe or TCC. However, if it turns out that it is too difficult to recruit 150 participants, the recruitment of participant will end when the primary end point (healing at 12 weeks) has been observed for 56 participants per group, giving a total of 112 which fulfils the sample size calculation.

2.4 FRAMEWORK

The primary outcome will be tested according to the non-inferiority hypothesis testing framework. All secondary outcomes will be tested according to the superiority hypothesis testing framework.

2.5 STATISTICAL INTERIM ANALYSES AND STOPPING GUIDANCE

One interim analysis will be conducted after the primary outcome (proportion of healed ulcers at 12 weeks) has been observed in 30 participants in each study arm. The analysis will be conducted according to the intention-to-treat (ITT) approach, that is, all participants randomized will be analyzed according to their intended study group. If a two-sided Chi-square test demonstrates a statistically significant difference between the groups on the 0.001 level (relative risk, risk difference and odds ratio (OR) with confidence intervals (CI) will also be calculated) recruitment of new participants will be stopped but the follow-up of participants who already are enrolled in the study will continue. If the Chi-square test is not significant (that is, p>0.001), recruitment of new participants will continue as planned. The significance level will not be adjusted due to the interim analysis as only one interim analysis is conducted.

2.6 TIMING OF FINAL ANALYSIS

The short-term outcomes, that is, healing, adverse events and adverse device effects during treatment, will be analyzed and published after the required number of participants have ended the treatment period.
The long-term outcomes, that is, up to 12 months after treatment end, will be analyzed and published after that every included participant has either been assessed for 12 months outcomes or has been lost to follow-up.

2.7 TIMING OF OUTCOME ASSESSMENTS

Table 1 below lists outcomes and time points for assessments (base-line, 4 weeks into treatment, and 1, 6 and 12 months after treatment end). For the 4 week into treatment and 1 month post-treatment assessments, a visit window of ±1 week will be used. For the 6 and 12 months post-treatment assessments, a visit window of ±1 month will be used.

Table 1. Overview of variables and assessment methods.

Variable (scale level: nominal=N, ordinal=O, interval=I)	Assessment method	Assessment occasion				
		Treatment period		Follow-up after treatment end		
		Base-line	4 weeks	1 month	6 months	12 months
Ulcer healing (N)	Clinical observation + blinded photo	X	X	X		
Skin complications (N)	Clinical observation + blinded photo	X	X	X		
Glycemic control (I)	Blood sample (HbA1c) [a]	X	X	X	X	X
BMI (I)	Measurement of weight and height	X	X	X	X	X
Gait function (I)	10 meter walk test[b] [17]	X	X	X	X	X
Gait function (I)	Timed up and go[b] [18]	X	X	X	X	X
Balance (O)	Berg balance scale[b] [19]	X	X	X	X	X
Muscle atrophy (I)	Calf circumference[a] [20]	X	X	X	X	X
General quality of life (O)	RAND-36[c] [21], EQ-5D-5L[c] [22]	X	X	X	X	X
Disease-specific quality of life (O)	DFS-SF[c] [23]	X	X	X	X	X
Physical activity (I)	ActivPAL[d] [24]	X	X	X	X	X
Physical activity (O)	National Board of Health and Welfare's indicator questions[25]	X	X	X	X	X
Bone mass density (I)	DXA[e] (heel bone)	X		X	X	X
Locus of control (O)	Questions from MHLC-C[c] [26]	X		X	X	X
Ankle range of motion (I)	Goniometer [a] [27]	X		X	X	X
Ankle strength (I)	Dynamometer [a] [28]	X		X	X	X
Adherence to therapeutic shoes (O)	Questions from Q-TFA [c] [29]	X		X	X	X
Treatment satisfaction (O)	Visual analogue scale[c]		X	X		
New ulcers, amputations, death, Charcot foot (N)	Patient file and self-report [c]				X	X
Health care consumption (O)[f]	Patient administration systems and self-report[c]				X	X	X
Sick leave from work (I) [f]	Self-report,[c] Swedish Social Insurance Agency's system			X	X	X

[a]Standardized method, [b]function test, [c]questionnaire, [d]activity monitor, [e]Dual-energy X-ray absorptiometry [f]for the of health-economic analysis.

3 STATISTICAL PRINCIPLES

3.1 CONFIDENCE INTERVALS AND P VALUES

In all analyses a 95% confidence level will be used as a cut off to declare statistical significance, and report both exact p-values and 95% CI. One-sided tests and CI will be used for the primary outcome and two-sided tests and CI the secondary outcomes. No adjustment for multiple comparisons will be used.

3.2 ADHERENCE AND PROTOCOL DEVIATIONS

Adherence to the interventions (sealed shoe and TCC) is defined as continuous use of the devices during the treatment period. If a person treated with TCC removes the device on one or more occasions or refuses to continue treatment this will be considered non-adherence. If a person treated with a sealed shoe removes the device (assessed by inspecting if the seal has been broken) on one or more occasions or refuses to continue treatment this will be considered non-adherence.
Non-adherence will be presented per type of non-adherence and frequency. All types of non-adherence will be presented as number and percentage. In addition, removal of devices will be presented as means and standard deviation.

A protocol deviation is defined as a failure to adhere to the protocol such as the wrong intervention being administered, incorrect data being collected and documented, errors in applying inclusion/exclusion criteria or missed follow-up visits. This will be presented as number and type, per study group.

3.3 ANALYSIS POPULATIONS

The primary outcome (ulcer healing) will be analyzed both on the ITT dataset, that is, on all randomized participants, and on the per protocol dataset, including only patients who were exposed to the intended intervention at least 80% of the treatment days, as judged per above (point 3.2). Secondary outcomes (including adverse events and adverse device effects) will only be analyzed on the ITT dataset.

4 STUDY POPULATION

4.1 SCREENING DATA

The following summaries will be presented for all screened patients:
Enrolment: the number of patients screened, the number of patients recruited, and the reason for non-recruitment.

4.2 ELIGIBILITY

All patients attending the multidisciplinary diabetic foot teams at the study centers during the screening period will be assessed for eligibility.

Inclusion criteria: at least 18 years old, diagnosed diabetes mellitus (all types) and foot ulcer under metatarsal heads. A foot ulcer is here defined as "a break of the skin of the foot that includes minimally the epidermis and part of the dermis."[30]

Exclusion criteria: large ulcers (covering 3-5 metatarsal heads), toe pressure or TcPO2 <30 mmHg, infection of IWGDF grade 3 (if uncontrolled or treatment has not been administered) or IWGDF grade 4, life expectancy <1 year, active Charcot foot, need of custom-made shoe, and inability to read or write Swedish. In addition, people will be excluded where dementia, language- or other communication difficulties, active alcohol or substance abuse, or other factors increase the risk that adverse events or adverse device effects will not be noted or reported, if the person does not have adequate social support.

The eligibility data will be summarized as number of patients screened, number of patients who fulfilled the inclusion criteria, and the number of the patients fulfilling the inclusion criteria that were excluded due to violating each exclusion criterion or who declined to participate. In addition, the number of ineligible patients randomized, if any, will be reported, with reasons for ineligibility.

4.3   RECRUITMENT

Information required by the CONSORT flow diagram will be collected and presented: number of patients screened, number who were excluded (per reason) and number who declined to participate, number of patients randomized, number of participants who were allocated to each study group, number who received the allocated intervention and number who did not receive the allocated intervention (per reason and study group), number who discontinued intervention or were lost to follow-up (per reason, per follow-up visit and per study group), number who were analyzed and excluded from analysis (per reason and study group).

4.4   WITHDRAW / FOLLOW-UP

There are several timings of possible withdrawal/lost to follow-up: before base-line assessment, before the intervention has been administered, during the intervention period, and before each follow-up assessment. Reasons include, but are not restricted to, clinical reasons, death, refusal to continue treatment or follow-up, unable to make contact with the participant, etc.
Number of participants, reasons and timing of withdrawal/lost to follow-up will be presented by intervention arm in a CONSORT flow diagram (point 4.3)

5   STUDY ASSESSMENTS

5.1   BASELINE PATIENT CHARACTERISTICS

Baseline characteristics that will be summarized include: sex, age, education level, living conditions (living alone, with partner, children, etc.), diabetes type and duration, glycemic control, body mass index (BMI), history of previous foot ulcers and amputations, foot deformities, index foot ulcer characteristics (site, area, depth, duration, infection grade), number of active ulcers, use of tobacco, peripheral artery disease (toe pressure, TcPO2), and neuropathy (assessed with Ipswitch Touch Test and Vibratip). Categorical data will be summarized as n (%).
Continues data will be summarized as mean (standard deviation).

5.2 EFFICACY ASSESSMENTS

5.2.1 PRIMARY EFFICACY ENDPOINT

Primary efficacy endpoint is ulcer healing at 12 weeks, defined as complete epithelialization which is maintained for a minimum of 14 days (as required by the US Food and Drug Administration, FDA)[31]. Ulcer healing will be assessed by the cast technician at the local hospital who redress the DFU, approximately 1-2 times per week (depending on the status of the DFU) in both groups. The cast technician will also photograph the DFU so it can be assessed by another person, blinded to group allocation.

5.2.2 SECONDARY EFFICACY ENDPOINTS

Secondary outcome measures (variables and assessment methods) are listed in Table 1. The cast technician will document and take photographs of skin complications. A physiotherapist will perform the standardized assessments (calf circumference, etc.) and function tests (gait, balance, etc.).

5.2.3 ADDITIONAL EFFICACY ENDPOINTS

Not applicable.

5.3 SAFETY ASSESSMENTS

5.3.1 ADVERSE EVENTS

Adverse events that are judged to be related to the offloading devices (shoe or TCC) will be classified as adverse device effects (ADE) and serious adverse device effects (SADE).[32] ADE include, but are not limited to, skin abrasions, blisters, sleep disturbances, issues with gait and balance, etc. SADE include, but are not limited to, new foot ulcers that result in amputation (major amputation = above ankle, minor amputation = below ankle), sepsis, etc.

Averse events that are not related to the offloading devices are classified as adverse events (AE) and serious adverse events (SAE).[32] AE include, but are not limited to, skin abrasions or new foot ulcers on the contralateral foot and not related to the device, etc. SAE include, but are not limited to, death, amputation, onset of acute Charcot foot, sepsis, etc. (not related to the offloading device). However, in accordance with previous studies on similar patient populations, not all AE and SAE will be included as the patient population suffers from multiple co-morbidities and therefore a high incidence of illness and hospital admissions unrelated to the DFU and offloading devices can be expected.[33] Therefore, all ADE and SADE will be assessed, but only certain types of AE and SAE that are of particular interest, such as, amputation, death and onset of acute Charcot foot.

ADE, SADE, AE and SAE will be assessed with the aid of questionnaires, CRF, photographs of ulcer and skin, and patient files.

5.3.2 CLINICAL LABORATORY ASSESSMENT

Not applicable.

5.3.3 OTHER SAFETY ASSESSMENT

Not applicable.

6 STATISTICAL ANALYSES

6.1 ANALYSIS METHODS

6.1.1 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Primary efficacy endpoint is ulcer healing at 12 weeks, defined as complete epithelialization which is maintained for a minimum of 14 days (as required by the FDA).[31] Healing is thus a single endpoint assessed on a nominal scale.

Ulcer healing will be assessed by the cast technician at the local hospital who redress the DFU, approximately 1-2 times per week (depending on the status of the DFU) in both groups. The cast technician will also photograph the DFU so it can be assessed by another person, blinded to group allocation.

In the analysis of the primary endpoint, the ITT dataset (analyzed with and without adjustment for covariates) and the per protocol dataset (analyzed without adjustment for covariates only) will be used. For the non-adjusted analyses, crude risk ratio (RR) or OR will be calculated to assess the impact of offloading device type on ulcer healing. For the adjusted analysis, baseline variables (sex, age, education level, living conditions, diabetes type and duration, glycemic control, BMI, history of previous foot ulcers and amputations, foot deformities, index foot ulcer characteristics, number of active ulcers, use of tobacco, peripheral artery disease, and neuropathy, see point 5.1) will be included as candidates in a logistic multiple regression, using backward selection and a p-value of 0.10 as cut-off for removal.

Participants for whom the 12 week observation is missing will be categorized as "not healed". The statistician conducting the analysis will be blinded to group allocation.

The proportion of healed ulcers in each study group will be calculated, and the results will be presented as RR or OR and corresponding 95% CI.

6.1.2 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The secondary analyses are not dependent on the findings of the primary endpoint. No adjustment for Type 1 errors will be used as only one or a few statistical tests will be conducted for each secondary endpoint.

The secondary endpoints are time to healing and measures listed in Table 1. Each secondary endpoint is measured between one and five occasions during the study. The ITT dataset will be used for all analyses of secondary endpoints. Adjusted analyses will only be conducted for certain secondary endpoints that are of particular interest.

Time to healing will be compared between the study groups using survival analysis. Kaplan-Meier survival curves will be produces for the two study groups with median healing times and 95 % CI. Participants for whom the ulcer has not healed will be treated as censored and their date of trial exit or date of last available assessment will be used to calculate their duration in the trial. Hazard ratio with

95% CIs will be presented. Treatment effect will be explored using a Cox proportional hazards model including stratification factors (ulcer area and depth at baseline, periphery artery disease and infection grade) initially.

Survival analysis as above (but without adjustment) will also be used to compare ulcer recurrence after healing between the study groups. Recurrence rates at 12 months after healing will also be compared.

The analysis of the other secondary endpoints will be conducted according to scale level (nominal, ordinal or interval; Table 1) and compared at each time point (base-line, 4 weeks into treatment and 1, 6 and 12 months post-treatment) using the ITT dataset without adjustment for covariates: t-tests for ordinal and interval data if the assumptions of the t-test if fulfilled (normal distribution and equal variances), otherwise Wilcoxon rank sum test will be used. The Chi-squared test or generalized linear regression method will be used for nominal scale data. For each comparison both exact p-values and two-sided 95% CI will be reported.

The health economic analysis will be a cost-utility analysis that compare the interventions (sealed shoe and cast): treatment costs, quality of life during and after treatment, sick leave from work, and health care consumption. Effects on quality of life will be assess with EQ-5D-5L and SF-36 that makes it possible to express effects on quality of life in terms of quality-adjusted life years. The perspective of the analysis will be societal and take effects from the treatment start to 12 month after treatment end into account. Questionnaires, patient administrative systems, and the Swedish Social Insurance Agency's system will be used as data sources.

6.1.3 SAFETY ANALYSES

Safety endpoints during the treatment period will be reported as summary statics (number and percentage) per study group. They will be categorized as AE, SAE, ADE and SADE (see point 5.3 above) and the proportions will be compared between the study groups with statistical tests for nominal scale data, that is, Chi-square test and presenting exact p-values and two-sided 95% CI.

6.1.4 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics will be summarized and presented for each study group, including demographic variables (sex, age, education level, living conditions, body mass index,), disease-related variables (diabetes type, diabetes during, glycemic control), foot-related variables (history of previous foot ulcers and amputations, foot deformities), index foot ulcer characteristics (site, ulcer area, depth, infection grade, duration), peripheral artery disease (toe pressure, TcPO2), neuropathy (assessed with Ipswitch Touch Test and Vibratip), and other variables (activity level, use of tobacco etc.).

Variables measured on a nominal scale will be presented as number (%), continues variables will be presented as mean (standard deviation).

6.1.5 SUB-GROUP ANALYSES

There is some debate whether non-removable offloading devices (such as TCC) are effective and safe to use for people with peripheral artery disease and infected DFU. For this reason, sub-group analyses will

be conducted for people with impaired circulation and more infected DFU at baseline, for the primary outcome (healing) and adverse events.

6.1.6 TABULATION OF INDIVIDUAL PARTICIPANT DATA

No individual participant data will be listed.

6.1.7 EXPLORATORY ANALYSES

Activity data will be collected with the ActivPAL activity monitor during 7 days after each of the 5 assessment visits to the physiotherapist. These data (on sitting, standing, walking, etc.) will mainly be analyzed in an exploratory manner, to investigate differences between study groups, trends over time, etc.

6.1.8 SENSITIVITY ANALYSES

The primary outcome will be analyzed on the ITT data set, per protocol dataset, and ITT dataset using multiple regression as a sensitivity analysis to test the robustness of the results. Multiple imputation will also be used as a sensitivity analysis for the primary outcome (see point 6.2).

6.2   MISSING DATA

Missing primary outcome data will be investigated through multiple imputation as a secondary sensitivity analysis of the primary outcome, as in previous study on devices for DFU healing.[33]

6.3   STATISTICAL SOFTWARE

Standard commercially available statistical software such as Stata, SPSS or R will be used for the analyses.

7   ABBREVIATIONS

AE	Adverse Event
ADE	Adverse Device Effects
BMI	Body Mass Index
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DFU	Diabetic Foot Ulcer
FDA	Food and Drug Administration
ITT	Intention-To-Treat
RR	Risk Ratio
OR	Odds Ratio
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effects
SAP	Statistical Analysis Plan
TCC	Total Contact Cast

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