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Health related quality of life in patients with diabetic foot ulceration: study protocol for adaptation and validation of PROM's (patient reported outcome measurements) in Dutch-speaking patients

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SCHOLARONE™
Manuscripts

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3 **Health related quality of life in patients with diabetic foot ulceration: study protocol for**
4 **adaptation and validation of PROM's (patient reported outcome measurements) in**
5 **Dutch-speaking patients**
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ABSTRACT

Introduction: Diabetic foot ulceration (DFU) is a common late-stage complication of diabetes with a large impact on health status and quality of life. Patient-reported outcome measures (PROMs) provide a standardized method of obtaining patients' views on their wellbeing. The DFU Scale Short Form (DFS-SF) is a validated disease-specific PROM for measuring health-related quality-of-life (HRQoL) among DFU patients. The Lower Extremity Functional Scale (LEFS) is another PROM that can be used to measure physical functioning in patients with lower extremity disorders. The LEFS is not yet validated for DFU. Both instruments are not validated in the Dutch language. The purpose of this study is to culturally adapt and validate the DFS-SF and LEFS questionnaires for Belgian Dutch speaking patients with DFU.

Methods and analysis: This study will be conducted as a monocenter observational cohort study in DFU patients presenting at a hospital based multidisciplinary diabetic foot clinic. Data will be collected from the medical electronic files and from DFS-SF, LEFS and EQ-5D-5L questionnaires that will be presented to the patients at defined time points. Reproducibility, internal consistency, floor and ceiling effects, construct validity, and responsiveness will be assessed for the DFS-SF and LEFS.

Ethics and dissemination: The study protocol has been approved by the Medical Ethics Committee of Onze-Lieve-Vrouw Hospital (Aalst, Belgium). The results of the study will be disseminated through peer-reviewed publications and conference presentations.

ARTICLE SUMMARY

Strengths and limitations of this study:

- Validated PROMs for DFU patients are much needed.
- Two PROMs are evaluated, one for measuring HRQoL (DFS-SF) and one for physical functioning (LEFS).
- This is the first study to evaluate the psychometric properties of LEFS in patients with DFU.
- This is the first study involves the validation of DFS-SF in Dutch speaking patients with DFU.
- Although this is a monocenter study, It will be conducted in a high volume hospital based multidisciplinary diabetic foot clinic

1. INTRODUCTION

Diabetic foot ulceration (DFU) is a common late-stage complication of diabetes, with 19-34% of individuals with diabetes experiencing a DFU in their lifetime [1]. These ulcers have a large impact on the health status and quality of life of the affected patients [2] and are associated with major health-care consumption and high costs [3,4]. They require intensive multidisciplinary treatment, and hospital admission rates for DFU exceed the rates for congestive heart failure, renal disease, depression and most forms of cancer [5].

In recent decades, understanding of the pathogenesis, treatment and prevention has improved [1]. In contrast, our knowledge of the impact of a foot ulcer on the quality of life of a diabetic patient is limited. This is nevertheless important, because the success of a long-term treatment and the compliance with preventive measures depend to a large extent on the mental resilience and motivation of the patient and on the patient's participation in his treatment.

PROMs are essential in evaluating quality of life and functional outcomes after application of a treatment as well as in clinical research [6]. PROMs can also be used in quality assessment of care across hospitals. Belgian hospital-based diabetes foot clinics are obligated to participate in IQED-Foot (Initiative for Quality improvement and Epidemiology in multidisciplinary Diabetic Foot Clinics), which includes audit-feedback cycles covering both processes and outcomes of care [7,8]. Data on quality of life are not included yet in this initiative, but may be used as a quality of care indicator for IQED-Foot in the future.

Literature on PROMs for DFU is limited. In a recent systematic review, based on an extensive search of available literature until September 2018, only 11 studies of appropriate quality were found [9]. A broader systematic review covering PROMs in the area of foot and ankle disease, also including studies on DFU, confirmed that the measurement properties of many instruments have been insufficiently studied and reported [10]. A valid Dutch version of a disease-specific PROM for DFU is currently not available.

A systematic review of the literature showed that the Diabetic Foot Ulcer Scale (DFS) is the most frequently used disease-specific PROM for measuring health-related quality-of-life (HRQoL) among diabetic foot patients [11]. This instrument was developed by using semi-structured interviews and focus groups of patients with DFUs and their caregivers [12]. It has

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3 shown internal consistency, reliability, validity and responsiveness to wound severity and
4 healing. A shortened version, the DFS Short Form (DFS-SF) showed similar robustness and
5 responsiveness compared to its original version [13], and is with 29 questions a more ‘user-
6 friendly ’ tool for everyday clinical practice. Despite its translation to several languages and
7 subsequent use in studies [14,15,16,17,18,19] its measurement properties have, however, not
8 yet been studied and reported across all the relevant dimensions of the COSMIN (COnsensus-
9 based Standards for the selection of health Measurement Instruments) Taxonomy of
10 Measurement Properties [20]. There are Dutch translations of DFS for Belgium and of DFS-
11 SF for the Netherlands available which have undergone a full linguistic process according to
12 the recognized methodology of translation as described in Linguistic Validation Manual for
13 Health Outcome Assessments [21]. This manual is the official guideline of the Mapi Institute,
14 owner of the copyright on the questionnaire. However, the measurement properties of these
15 questionnaires in a DFU population have not been evaluated yet in the Dutch language
16 versions.

17
18 PROM’s on physical functioning are available for lower extremity related pathologies such as
19 osteoarthritic conditions. However, most are not able to differentiate pain and function [22].
20 The Lower Extremity Functional Scale can distinguish between pain and function in a wide
21 variety of disorders [23,24]. The LEFS is validated in several languages, including in Dutch
22 for patients with osteoarthritis [25]. To our knowledge, the LEFS is not yet validated for
23 assessing functional impairment of foot and ankle in diabetic foot conditions.

24
25 In addition to the disease-specific PROMs measuring HRQoL and physical functioning
26 generic HRQoL instruments are also available. They collect information on the general
27 quality of life. They can be compared against data issued from the general population and
28 across pathologies. The EuroQol Five Dimension (EQ-5D) questionnaire is such a
29 standardized instrument consisting of five domains and a summary index. The 5-level EQ-5D
30 version (EQ-5D-5L) was introduced by the EuroQol Group in 2009 to improve the
31 instrument’s sensitivity and to reduce ceiling effects. The EQ-5D-5L is among the most
32 commonly used questionnaires for evaluating HRQoL [26]. Several studies support its
33 validity and reliability in many health related conditions such as DFU in different languages
34 [27,28,29].

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36 The aims of the study are the followings.

- 37 - To adapt and validate the Dutch DFS-SF questionnaire for evaluating the disease-specific
38 HRQoL of diabetic patients with a DFU.

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3 - To validate the Dutch LEFS questionnaire for evaluating the physical functioning of
4 diabetic patients with a DFU.
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8 **2. METHODS AND ANALYSIS**

9 **2.1 Study design**

10 This study will be conducted as a monocenter observational cohort study in Onze-Lieve-
11 Vrouw (OLV) Hospital Aalst. Data will be collected from the medical electronic files and
12 from DSF-SF, LEFS and EQ-5D-5L questionnaires that will be presented to the patients at
13 defined time points. Additional questions will be asked about loss of productivity (work
14 absenteeism), financial burden (out of pocket expenses), and satisfaction with the medical
15 treatment. There are no medical interventions, nor extra visits or laboratory tests planned
16 outside the normal clinical routine.
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19 The study will consist of 3 parts:
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22 Part 1: preparing the questionnaires.
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25 Minor linguistic adaptations will be made by research team to the Netherlands Dutch DFS-SF
26 and LEFS questionnaires to adapt them for Belgian native Dutch speaking patients. To clear
27 out linguistic ambiguities 10 patients will be asked if they understand the questions and are
28 able to provide answers. Based on their remarks small changes will be made if necessary.
29 Care will be taken to make only small linguistic changes that do not change the content of the
30 questionnaires. When changes are needed another group of 10 patients will be asked if they
31 understand the questions and are able to provide answers. This procedure will be repeated
32 until no changes are needed. At that point, the questionnaires are final and will not be adapted
33 anymore during the entire study.
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36 Part 2: testing reproducibility and measurements properties
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39 In order to determine the reproducibility (i.e., test-retest reliability) of the DSF-SF and LEFS
40 questionnaires fifty study participants will be asked to complete the questionnaires twice with
41 an interval of 2–3 weeks. This time interval needs to be sufficiently short for the patient's foot
42 condition to remain stable and sufficiently long to prevent remembrance of the answers to the
43 first questionnaire. Patients who underwent foot surgery or revascularization of the leg in this
44 time interval will be excluded. Patients will be asked about their subjective feeling of
45 presence or absence of change in their foot condition before completing the second
46 questionnaire: "Did the condition of your feet remain stable, compared with the last time you
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3 completed this questionnaire, yes or no?" Patients reporting a change will be excluded from
4 the analysis. Patients reporting no change will be considered stable between the two
5 measurements and are included for testing the reproducibility of the questionnaires.
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8 9 Part 3: testing measurement validity 10

11 Recruitment will continue until a sample size of at least 100 patients is reached (see sample
12 size calculations in section 2.8) for testing the measurement validity of the questionnaires. It
13 is estimated that this will take 2 years. All questionnaires will be administered at the first
14 presentation of patient on the diabetic foot clinic. The questionnaire will be re-administered at
15 moments of important treatment changes (eg before and after surgical treatment) or 6 months
16 after starting care (if the patient is still in follow-up) or at the moment of healing of a foot
17 ulcer when this takes less than 6 months.
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26 27 **2.2 Study population**

28 All consecutive patients attending the multidisciplinary outpatient clinic or being admitted at
29 OLV diabetic foot clinic, and who meet the inclusion criteria, will be invited to participate.
30 The recruitment of patients has started in April 2019.
31
32

33 The inclusion criteria are:
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- 35
36 ▪ adult patients ≥ 18 years
- 37
38 ▪ adequate comprehension of the Dutch to understand the questionnaires
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40 ▪ having a severe DFU (Wagner ≥ 2)
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42 ▪ attending the multidisciplinary outpatient diabetic foot clinic or admission to the
43 OLV inpatient diabetic foot department
- 44
45 ▪ able to provide written informed consent
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48 Patients with any of following criteria will be excluded from participation in the study:
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- 50
51 ▪ patient was not able to ambulate prior to DFU (ie, bedridden or wheelchair
52 dependent)
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54 ▪ cognitive dysfunction (which hampers the understanding of questionnaires)
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58 59 **2.3 Scoring Instruments** 60

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3 The DFS-SF consists of six conceptual domains (leisure, physical health, dependence/daily
4 life, negative emotions, worried about ulcers/feet, and bothered by ulcer care). The
5 questionnaire comprises of 29 items with a 5-point Liker rating scale. To create subscale
6 scores, all items are reverse coded so that higher values indicate better QoL [13].
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10 The LEFS consists of 20 items [24,25]. Items are rated on a 4-point scale, from 0 (extreme
11 difficulty/unable to perform activity) to 4 (no difficulty). The maximum possible score is 80
12 points, indicating very high function. The minimum possible score is 0 points, indicating very
13 low function .
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18 The EQ-5D-5L provides a scoring system producing a 'health state profile' comprising of five
19 different domains (Mobility, Self-care, Usual activities, Pain/Discomfort and
20 Anxiety/Depression). Each dimension is rated at five levels of severity, [no (level 1), slight
21 (level 2), moderate (level 3), severe (level 4), and extreme problems/unable (level 5)] [26].
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26 **2.4 Study setting**

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28 The questionnaires will be will be delivered digitally on a tablet. This is the preferential mode
29 of delivery.
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32 The patients will be instructed on how to use the tablet. Patients that find it difficult to use a
33 tablet will be assisted by a research nurse. The tablet will be provided to the patient before the
34 consultation in the waiting room. A physician from the diabetic foot clinic will perform the
35 physical examination.
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39 The following data will be collected from the standard medical files, based on the variables
40 included in IQED-Foot [7,8]: age, gender, comorbidities, diabetic foot related variables,
41 treatment related variables and outcomes of treatment. The ulcer will be assessed using the
42 PEDIS (Perfusion, Extent, Depth, Infection and Sensation) classification system. It includes
43 five ulcer criteria, and each criterion is graded by the severity [30].
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49 **2.5 Study duration**

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51 Patients will be followed for a total period of 6 months or until healing of an ulcer when this
52 takes less time. The study will continue until the sample size has been obtained.
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2.6 Statistical analysis

All data will be entered in a clinical database. The SAS 9.4 will be used to perform statistical analyses. The missing values will not be imputed, as the raw data for individual items would be analysed. Normality of continuous data will be tested with the Shapiro-Wilk test. Continuous data will be reported as mean \pm SE (parametric) or median with percentiles (non-parametric) and categorical data as numbers with percentages. Categorical variables will be assessed using χ^2 tests. Continuous data will be compared using Student's t-tests (parametric data) or Mann-Whitney U tests (non-parametric data).

2.7 Evaluation of measurements properties of DFS-SF and LEFS

The measurement properties of the Belgian-Dutch versions of the DFS-SF and LEFS will be assessed. The characteristics that will be assessed are based on the COSMIN Taxonomy of Measurement Properties [20] and the criteria for adequacy that will be used are based on publications by Terwee et al. [14], Mokkink et al. [31] and Heintjens et al. [32]. If the COSMIN Study Design checklist [33] is available before data collection ends, we will take into account any additional criteria mentioned in this checklist before starting the assessment of the measurement properties.

Reproducibility

Reproducibility consists of two parts: reliability and agreement. Reliability concerns the extent to which scores for patients who have not changed are the same for repeated measurement under several conditions. Evaluation of the test-retest reliability will be performed by calculating the intraclass correlation coefficient (ICC agreement) with a corresponding 95% CI. Reliability will be given a positive rating when the ICC is at least 0.70 in a sample size of 50 patients.

Agreement concerns the absolute measurement error, that is, how close the scores on repeated measures are. The degree of absolute agreement will be expressed as the SE of measurement (SEM agreement). This SEM equals the square root of the error variance of an analysis of variance analysis, including the systematic differences ($SEM = \sqrt{(\text{variance}_{\text{patient}} + \text{variance}_{\text{residual}})}$). A sample size of at least 50 patients is considered as adequate for the assessment of the agreement parameter, based on a general guideline by Altman [34].

Internal consistency

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3 Internal consistency is defined as the extent to which items in a (sub)scale are intercorrelated,
4 thus measuring the same construct. The correlation between items on a (sub)scale will be
5 evaluated by calculating Cronbach's α for every (sub)scale. Internal consistency is
6 considered sufficient if the value for Cronbach's α is between 0.70 and 0.95, provided that
7 the scale is unidimensional. Regarding the number of subjects to include, rules-of-thumb vary
8 from four to 10 subjects per variable, with a minimum number of 100 subjects to ensure
9 stability of the variance-covariance matrix [34].
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15 16 **Floor and ceiling effects**

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18 Floor and ceiling effects will be determined by calculating the number of individuals who
19 obtained the lowest (floor) or highest (ceiling) possible scores and will be considered present
20 if more than 15% of the respondents achieved the lowest or highest score in a sample size of
21 at least 50 patients.
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26 27 **Construct validity**

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29 In order to evaluate the construct validity of DFU-FS and LEFS, we will use a set of
30 hypotheses between the instruments scores (convergent validity) and the population
31 characteristics or treatments (discriminative validity). In the literature, a positive rating for
32 construct validity is given if hypotheses are specified in advance and at least 75% of the
33 results are in correspondence with these hypotheses, in (sub) groups of at least 50 patients
34 [35]. Pearson's product-moment correlation coefficients (parametric data) or Spearman's r
35 (rank correlation) coefficients (non-parametric data) will be calculated. Correlation
36 coefficients above 0.6, between 0.6 and 0.3 and <0.3 will be considered high, moderate an
37 low correlations, respectively. We will use Student's t-tests (parametric data) or Mann-
38 Whitney U tests (non-parametric data) to compare two groups of patients based on their
39 characteristics.
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48 We propose the following hypotheses:
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51 For the LEFS:

- 52 1. patients with bilateral foot lesions (ulcer and/or active Charcot and/or previous leg
53 amputation) demonstrate lower LEFS scores than patients with unilateral foot lesions.
- 54 2. patients with only plantar foot ulcers demonstrate lower LEFS scores than patients with
55 only non-plantar foot ulcers
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3. patient with only toe wounds demonstrate higher LEFS scores than patients with wounds at other locations of the foot.
4. there is a moderate negative correlation ($r=0.3-0.6$) between the LEFS score and the PEDIS score of the most severe foot ulcer.
5. patients with bone involvement (PEDIS D3) demonstrate lower LEFS scores than patients without bone involvement
6. patients with peripheral artery disease (PEDIS P2 and 3) demonstrate lower LEFS scores than patients without peripheral artery disease (PEDIS P1)

For the DFS-SF:

1. patients with bilateral foot lesions (ulcer and/or active Charcot and/or previous leg amputation) demonstrate lower DFS-SF scores than patients with unilateral foot lesions.
2. patients with only plantar foot ulcers demonstrate lower DFS-SF scores than patients with only non-plantar foot ulcers.
3. patient with only toe wounds demonstrate higher DFS-SF scores than patients with wounds at other locations of the foot.
4. there is a moderate negative correlation ($r=0.3-0.6$) between the DFS-SF score and the PEDIS score of the most severe foot ulcer.
5. patients with bone involvement (PEDIS D3) demonstrate lower DFS-SF scores than patients without bone involvement
6. patients with peripheral artery disease (PEDIS P2 and 3) demonstrate lower DFS-SF scores than patients without peripheral artery disease (PEDIS P1)

Criterion validity

Criterion validity refers to the extent to which scores on a particular instrument relate to a gold standard. EQ5D has been used in several pivotal studies in patients with DFU [36,37,38]. HRQoL scores will be measured at baseline and at 6 months (defined as 4 to 8 months). To evaluate the performance of DSF-SF, results of DFS-SF and EQ-5D will be correlated at the level of individual patients using Pearson or Spearman rank correlation techniques. In addition changes in the different domains of DFS-SF will be compared with changes in EQ-5D.

Responsiveness

Responsiveness is defined as the ability of a questionnaire to detect clinically important changes over time, even if these changes are small. The DSF-SF and LEFS questionnaires will be administered at baseline, at 6 months and at the moment of healing. Changes over time will be analyzed by calculating the differences between the three different time points for all questionnaire domains.

2.8 Sample size considerations

This study will test multiple hypotheses related to the following instruments: DFS-SF, LEFS and EQ-5D. Because the LEFS has not yet been used in the context of the diabetic foot, we cannot estimate sample size based on previously reported data using this instrument.

We estimated sample size at $\alpha = 0.05$ and power of at least 80%, as calculated by PROC POWER (SAS 9.4).

In the context of construct validity, we identified the following previously reported cross-sectional associations.

First, Kontodimopoulos et al. [38] reported associations of DFS-SF subscale scores with ulcer depth, graded as superficial, deep and up to bone. According to the group means and standard deviations reported by the authors, and assuming the ulcer depth distribution observed in IQED-Foot (14, 56, and 30% superficial, deep and up to bone respectively [7]), the estimated sample size is 100 patients for all subscales to detect a significant overall difference between the three groups with one-way ANOVA.

Second, Macioch et al. [39] reported Spearman rank correlation coefficients between DFS-SF subscales and PEDIS ulcer classification. The strongest correlation was between the “Dependence/daily life” subscale and PEDIS perfusion grade, with a correlation coefficient of -0.312. The estimated sample size to obtain a similar correlation coefficient was 78 patients.

Next, in the context of criterion validity (association of DFS-SF with EQ-5D), we identified no publications to which we could compare to estimate sample size.

Finally, in the context of responsiveness we identified a number of publications reporting mean and standard deviations both for DFS-SF and EQ-5D, but the follow-up was not always 6 months. We estimated sample size for a paired t-test according to 5 different scenarios, depending on the extent to which within-patient scores were correlated over time: a correlation of 0, 0.25, 0.50, 0.75 or 1.

Spanos et al. [40] reported the change in DFS-SF subscale scores after 12 months. The estimated sample size range was 3-56 for the subscale with the lowest mean difference. The highest sample size is that needed in the hypothetical case that a patients' score was completely uncorrelated between 0 and 12 months.

Holman et al. [41] reported the change in EQ-5D index score after 24 weeks. The estimated sample size range was 3-177.

Li et al. [42] reported the change in EQ-5D index score after 12 weeks. We used data from the control group. The estimated sample size range was 7-123.

Siersma et al. [43] reported the change in EQ-5D index score after 12 months, separately for patients whose DFU healed within 6 months of follow-up, after 6 months of follow-up or whose DFU did not heal within 12 months. The estimated sample size range was 4-134, 3-129, 3-720 for group 1, 2 and 3 respectively.

In conclusion, a sample size of 100 patients seems sufficient to detect the most pronounced cross-sectional associations reported in the literature, among the set of associations that we are able to replicate in our study. With regard to the longitudinal change of HRQoL, there are no studies on the DFS-SF using a 6-month follow-up. Based on the use of EQ-5D, we can only compare to the study by Holman et al.: in the worst case scenario, the sample size needed to detect a similar difference in HRQoL would be 177 patients. At a moderate within-patient correlation of 0.5, the sample size needed would be only 90 patients, well within the recruitment potential of the proposed study.

2.9 Patient and Public Involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination of our research.

3. ETHICS AND DISSEMINATION

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3 Enrolment in this study does not have any influences on treatment. Verbal and written
4 information including an information letter and an informed consent form will be given by a
5 research physician or research nurses. Patients can always withdraw consent for inclusion of
6 their data in the analysis.
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10 The trial will be conducted in compliance with the principles of the Declaration of Helsinki
11 (2013), the principles of GCP and in accordance with all applicable regulatory requirements.
12 This protocol and related documents were approved by the Medical Ethics Committee of
13 OLV Aalst (Belgian registration number B126201836509). The Investigator and the
14 Participating Site shall treat all information and data relating to the Study disclosed to
15 Participating Site and/or Investigator in this Study as confidential and shall not disclose such
16 information to any third parties or use such information for any purpose other than the
17 performance of the Study. The collection, processing and disclosure of personal data, such as
18 patient health and medical information is subject to compliance with General Data Protection
19 Regulation (Directive 95/46/EC, Regulation (EU) 2016/679 of the European Parliament and
20 of the Council of 27 April 2016 on the protection of natural persons with regard to the
21 processing of personal data and on the free movement). The collected data will be coded. The
22 clinical team will protect the data from disclosure outside the research.
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33 The subject's name or other identifiers will be stored separately (site file) from their research
34 data and replaced with a unique code to create a new identity for the subject. The research
35 team will only have access to the coded research data.
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39 The results of the study will be disseminated through peer-reviewed publications and
40 conference presentations. If available at the time of publication, the results will be reported in
41 accordance with the COSMIN Reporting checklist, which is a checklist that is still under
42 development and will provide reporting guidelines for studies on measurement properties of
43 PROMs [44].
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49 **4. CONCLUSION, STRENGTHS AND LIMITATIONS:**

50 Validated PROMs for DFU patients are much needed. We propose a study that evaluates two
51 PROMS, one for measuring HRQoL (DFS-SF) and one for physical functioning (LEFS). It is
52 the first study of LEFS in patients with DFU and the first study of DFS-SF in Dutch speaking
53 patients with DFU. It is a monocenter study, but performed in a high volume hospital based
54 multidisciplinary diabetic foot clinic.
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60 **5. AUTHORS CONTRIBUTIONS**

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3 WR and FN developed the study. WR will act as a principal investigator. WR, FML, KD, GM
4 and FN were involved in writing the study protocol. WR, FML, KD, GM and FN will be
5 involved in assessment of outcomes. FML and KD will perform statistical analysis of the
6 study data. WR and FN drafted the manuscript.
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10 11 12 **6. FUNDING STATEMENT**

13
14 This research received no specific grant from any funding agency in the public, commercial or
15 not-for-profit sectors'.
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18 19 20 **7. CONFLICTS OF INTERESTS**

21 The authors declare no financial support from any organisation for the submitted work.
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24 25 26 **8. DATA AVAILABILITY STATEMENT**

27 All data relevant to the study are included in the article.
28
29

30 31 32 **9. REFERENCES**

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Health related quality of life in patients with diabetic foot ulceration: study protocol for adaptation and validation of PROM's (patient reported outcome measurements) in Dutch-speaking patients

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3 **Health related quality of life in patients with diabetic foot ulceration: study protocol for**
4 **adaptation and validation of PROM's (patient reported outcome measurements) in**
5 **Dutch-speaking patients**
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ABSTRACT

Introduction: Diabetic foot ulceration (DFU) is a common late-stage complication of diabetes with a large impact on health status and quality of life. Patient-reported outcome measures (PROMs) provide a standardized method of obtaining patients' views on their wellbeing. The DFU Scale Short Form (DFS-SF) is a validated disease-specific PROM for measuring health-related quality-of-life (HRQoL) among DFU patients. The Lower Extremity Functional Scale (LEFS) is another PROM that can be used to measure physical functioning in patients with lower extremity disorders. The LEFS is not yet validated for DFU. Both instruments are not validated in the Dutch language. The purpose of this study is to culturally adapt and validate the DFS-SF and LEFS questionnaires for Belgian Dutch speaking patients with DFU.

Methods and analysis: This study will be conducted as a monocenter observational cohort study in DFU patients presenting at a hospital based multidisciplinary diabetic foot clinic. Data will be collected from the medical electronic files and from DFS-SF, LEFS and EQ-5D-5L questionnaires that will be presented to the patients at defined time points. Reproducibility, internal consistency, floor and ceiling effects, construct validity, and responsiveness will be assessed for the DFS-SF and LEFS.

Ethics and dissemination: The study protocol has been approved by the Medical Ethics Committee of Onze-Lieve-Vrouw Hospital (Aalst, Belgium). The results of the study will be disseminated through peer-reviewed publications and conference presentations.

ARTICLE SUMMARY

Strengths and limitations of this study:

- This is the first study, which aims to validate the Diabetic Foot Ulcer Scale Short Form (DFS-SF) and the Lower Extremity Functional Scale (LEFS) into Dutch.
- The proposed study conforms to the COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) guidelines.
- This is a prospective monocentre observational study, which will be conducted in a high volume hospital based multidisciplinary diabetic foot clinic.
- Although the study will be applicable in Dutch-speaking regions in Belgium and the Netherlands, it is also relevant and informative for other regions

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3 - The study is limited to adults who have a severe DFU (Wagner ≥ 2) and were able to
4 ambulate prior to developing DFU.
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16 **1. INTRODUCTION**

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18 Diabetic foot ulceration (DFU) is a common late-stage complication of diabetes, with 19-34%
19 of individuals with diabetes experiencing a DFU in their lifetime [1]. These ulcers have a
20 large impact on the health status and quality of life of the affected patients [2] and are
21 associated with major health-care consumption and high costs [3,4]. They require intensive
22 multidisciplinary treatment, and hospital admission rates for DFU exceed the rates for
23 congestive heart failure, renal disease, depression and most forms of cancer [5].
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27 In recent decades, understanding of the pathogenesis, treatment and prevention has improved
28 [1]. In contrast, our knowledge of the impact of a foot ulcer on the quality of life of a diabetic
29 patient is limited. This is nevertheless important, because the success of a long-term treatment
30 and the compliance with preventive measures depend to a large extent on the mental
31 resilience and motivation of the patient and on the patient's participation in his treatment.
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35 PROMs are essential in evaluating quality of life and functional outcomes after application of
36 a treatment as well as in clinical research [6]. PROMs can also be used in quality assessment
37 of care across hospitals. Belgian hospital-based diabetes foot clinics are obligated to
38 participate in IQED-Foot (Initiative for Quality improvement and Epidemiology in
39 multidisciplinary Diabetic Foot Clinics), which includes audit-feedback cycles covering both
40 processes and outcomes of care [7,8]. Data on quality of life are not included yet in this
41 initiative, but may be used as a quality of care indicator for IQED-Foot in the future.
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51 Literature on PROMs for DFU is limited. In a recent systematic review, based on an extensive
52 search of available literature until September 2018, only 11 studies of appropriate quality
53 were found [9]. A broader systematic review covering PROMs in the area of foot and ankle
54 disease, also including studies on DFU, confirmed that the measurement properties of many
55 instruments have been insufficiently studied and reported [10]. A valid Dutch version of a
56 disease-specific PROM for DFU is currently not available.
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3 A systematic review of the literature showed that the Diabetic Foot Ulcer Scale (DFS) is the
4 most frequently used disease-specific PROM for measuring health-related quality-of-life
5 (HRQoL) among diabetic foot patients [11]. This instrument was developed by using semi-
6 structured interviews and focus groups of patients with DFUs and their caregivers [12]. It has
7 shown internal consistency, reliability, validity and responsiveness to wound severity and
8 healing. A shortened version, the DFS Short Form (DFS-SF) showed similar robustness and
9 responsiveness compared to its original version [13], and is with 29 questions a more ‘user-
10 friendly’ tool for everyday clinical practice. Despite its translation to several languages and
11 subsequent use in studies [14,15,16,17,18,19] its measurement properties have, however, not
12 yet been studied and reported across all the relevant dimensions of the COSMIN (COnsensus-
13 based Standards for the selection of health Measurement Instruments) Taxonomy of
14 Measurement Properties [20]. There are Dutch translations of DFS for Belgium and of DFS-
15 SF for the Netherlands available which have undergone a full linguistic process according to
16 the recognized methodology of translation as described in Linguistic Validation Manual for
17 Health Outcome Assessments [21]. This manual is the official guideline of the Mapi Institute,
18 owner of the copyright on the questionnaire. However, the measurement properties of these
19 questionnaires in a DFU population have not been evaluated yet in the Dutch language
20 versions.
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24 PROM’s on physical functioning are available for lower extremity related pathologies such as
25 osteoarthritic conditions. However, most are not able to differentiate pain and function [22].
26 The Lower Extremity Functional Scale can distinguish between pain and function in a wide
27 variety of disorders [23,24]. The LEFS is validated in several languages, including in Dutch
28 for patients with osteoarthritis [25]. To our knowledge, the LEFS is not yet validated for
29 assessing functional impairment of foot and ankle in diabetic foot conditions.
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32 In addition to the disease-specific PROMs measuring HRQoL and physical functioning
33 generic HRQoL instruments are also available. They collect information on the general
34 quality of life. They can be compared against data issued from the general population and
35 across pathologies. The EuroQol Five Dimension (EQ-5D) questionnaire is such a
36 standardized instrument consisting of five domains and a summary index. The 5-level EQ-5D
37 version (EQ-5D-5L) was introduced by the EuroQol Group in 2009 to improve the
38 instrument’s sensitivity and to reduce ceiling effects. The EQ-5D-5L is among the most
39 commonly used questionnaires for evaluating HRQoL [26]. Several studies support its
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3 validity and reliability in many health related conditions such as DFU in different languages
4 [27,28,29].

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6 The aims of the study are the followings.

- 7
8 - To adapt and validate the Dutch DFS-SF questionnaire for evaluating the disease-specific
9 HRQoL of diabetic patients with a DFU.
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11 - To validate the Dutch LEFS questionnaire for evaluating the physical functioning of
12 diabetic patients with a DFU.
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17 **2. METHODS AND ANALYSIS**

18 **2.1 Study design**

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20 This study will be conducted as a monocenter observational cohort study in Onze-Lieve-
21 Vrouw (OLV) Hospital Aalst. Data will be collected from the medical electronic files and
22 from DSF-SF, LEFS and EQ-5D-5L questionnaires that will be presented to the patients at
23 defined time points. Additional questions will be asked about loss of productivity (work
24 absenteeism), financial burden (out of pocket expenses), and satisfaction with the medical
25 treatment. There are no medical interventions, nor extra visits or laboratory tests planned
26 outside the normal clinical routine.
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32 The study will consist of 3 parts:

33 **Part 1: preparing the questionnaires**

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35 Minor linguistic adaptations will be made by research team to the Netherlands Dutch DFS-SF
36 and LEFS questionnaires to adapt them for Belgian native Dutch speaking patients.
37

38 To clear out linguistic ambiguities 10 patients will be asked if they understand the questions
39 and are able to provide answers. Based on their remarks small changes will be made if
40 necessary. Care will be taken to make only small linguistic changes that do not change the
41 content of the questionnaires. When changes are needed another group of 10 patients will be
42 asked if they understand the questions and are able to provide answers. If this is the case, no
43 further adaption to the questionnaire will be necessary. If there are ambiguities for the
44 patients, the adaptation procedure of the questionnaire will be repeated until no changes are
45 needed. At that point, the questionnaires are final and will not be changed anymore during the
46 entire study.
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57 **Part 2: testing reproducibility and measurements properties**

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3 In order to determine the reproducibility (i.e., test-retest reliability) of the DSF-SF and LEFS
4 questionnaires fifty study participants will be asked to complete the questionnaires twice. This
5 time interval needs to be sufficiently short for the patient's foot condition to remain stable and
6 sufficiently long to prevent remembrance of the answers to the first questionnaire. We
7
8 consider an interval of 2 to 3 weeks between completing of two questionnaires. Patients who
9
10 underwent foot surgery or revascularization of the leg in this time interval will be excluded.
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14 Patients will be asked about their subjective feeling of presence or absence of change in their
15 foot condition before completing the second questionnaire. They will be asked: "Did the
16 condition of your feet remain stable, compared with the last time you completed this
17 questionnaire, yes or no?" Patients reporting a change will be excluded from the analysis.
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19 Patients reporting no change will be considered stable between the two measurements and are
20 included for testing the reproducibility of the questionnaires.
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24 25 **Part 3: testing measurement validity**

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28 Recruitment will continue until a sample size of at least 100 patients is reached (see sample
29 size calculations in section 2.8) for testing the measurement validity of the questionnaires. It
30 is estimated that this will take 2 years.
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34 All questionnaires will be administered at the first presentation of patient on the diabetic foot
35 clinic. The patients will be asked to complete the questionnaire again at moments of important
36 treatment changes (eg before and after surgical treatment) or 6 months after starting care (if
37 the patient is still in follow-up) or at the moment of healing of a foot ulcer when this takes less
38 than 6 months.
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45 **2.2 Study population**

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47 All consecutive patients attending the multidisciplinary outpatient clinic or being admitted at
48 OLV Hospital diabetic foot clinic, and who meet the inclusion criteria, will be invited to
49 participate. The recruitment of patients has started in April 2019. The inclusion of the patients
50 expected to be completed by the end of 2020. The follow up of patients will end in June 2021.
51
52 The inclusion criteria are:
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- 55
56 ▪ adult patients ≥ 18 years
- 57
58 ▪ adequate comprehension of the Dutch to understand the questionnaires
- 59
60 ▪ having a severe DFU (Wagner ≥ 2)

- attending the multidisciplinary outpatient diabetic foot clinic or admission to the OLV inpatient diabetic foot department
- able to provide written informed consent

Patients with any of following criteria will be excluded from participation in the study:

- patient was not able to ambulate prior to DFU (ie, bedridden or wheelchair dependent)
- cognitive dysfunction (which hampers the understanding of questionnaires)

2.3 Scoring Instruments

The DFS-SF consists of six conceptual domains (leisure, physical health, dependence/daily life, negative emotions, worried about ulcers/feet, and bothered by ulcer care). The questionnaire comprises of 29 items with a 5-point Likert rating scale. To create subscale scores, all items are reverse coded so that higher values indicate better QoL [13].

The LEFS consists of 20 items [24,25]. Items are rated on a 4-point scale, from 0 (extreme difficulty/unable to perform activity) to 4 (no difficulty). The maximum possible score is 80 points, indicating very high function. The minimum possible score is 0 points, indicating very low function .

The EQ-5D-5L provides a scoring system producing a 'health state profile' comprising of five different domains (Mobility, Self-care, Usual activities, Pain/Discomfort and Anxiety/Depression). Each dimension is rated at five levels of severity, [no (level 1), slight (level 2), moderate (level 3), severe (level 4), and extreme problems/unable (level 5)] [26].

2.4 Study setting

The questionnaires will be delivered digitally on a tablet. This is the preferential mode of delivery.

The patients will be instructed on how to use the tablet. A research nurse will assist patients that find it difficult to use a tablet. The tablet will be provided to the patient before the consultation in the waiting room. A physician from the diabetic foot clinic will perform the physical examination.

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3 The following data will be collected from the standard medical files, based on the variables
4 included in IQED-Foot [7,8]: age, gender, comorbidities, diabetic foot related variables,
5 treatment related variables and outcomes of treatment. The ulcer will be assessed using the
6 PEDIS (Perfusion, Extent, Depth, Infection and Sensation) classification system. It includes
7 five ulcer criteria, and each criterion is graded by the severity [30].
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12 **2.5 Study duration**

14 Patients will be followed for a total period of 6 months or until healing of an ulcer when this
15 takes less time. The study will continue until the sample size has been obtained.
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18 **2.6 Statistical analysis**

21 All data will be entered in a clinical database. The SAS 9.4 will be used to perform statistical
22 analyses. The missing values will not be imputed, as the raw data for individual items would
23 be analysed. Normality of continuous data will be tested with the Shapiro-Wilk test.
24 Continuous data will be reported as mean \pm SE (parametric) or median with percentiles (non-
25 parametric) and categorical data as numbers with percentages. Categorical variables will be
26 assessed using χ^2 tests. Continuous data will be compared using Student's t-tests (parametric
27 data) or Mann-Whitney U tests (non-parametric data).
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34 **2.7 Evaluation of measurements properties of DFS-SF and LEFS**

36 The measurement properties of the Belgian-Dutch versions of the DFS-SF and LEFS will be
37 assessed. The characteristics that will be assessed are based on the COSMIN Taxonomy of
38 Measurement Properties [20] and the criteria for adequacy that will be used are based on
39 publications by Terwee et al. [14], Mokkink et al. [31] and Heintjens et al. [32]. If the COSMIN
40 Study Design checklist [33] is available before data collection ends, we will take into account
41 any additional criteria mentioned in this checklist before starting the assessment of the
42 measurement properties.
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49 **Reproducibility**

51 Reproducibility consists of two parts: reliability and agreement. Reliability concerns the
52 extent to which scores for patients who have not changed are the same for repeated
53 measurement under several conditions. Evaluation of the test-retest reliability will be
54 performed by calculating the intraclass correlation coefficient (ICC agreement) with a
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3 corresponding 95% CI. Reliability will be given a positive rating when the ICC is at least 0.70
4 in a sample size of 50 patients.
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7 Agreement concerns the absolute measurement error, that is, how close the scores on repeated
8 measures are. The degree of absolute agreement will be expressed as the SE of measurement
9 (SEM agreement). This SEM equals the square root of the error variance of an analysis of
10 variance analysis, including the systematic differences ($SEM = \sqrt{\text{variance}_{\text{patient}} + \text{variance}_{\text{residual}}}$). A sample size of at least 50 patients is considered as adequate for the
11 assessment of the agreement parameter, based on a general guideline by Altman [34].
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18 **Internal consistency**

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20 Internal consistency is defined as the extent to which items in a (sub)scale are intercorrelated,
21 thus measuring the same construct. The correlation between items on a (sub)scale will be
22 evaluated by calculating Cronbach's α for every (sub)scale. Internal consistency is
23 considered sufficient if the value for Cronbach's α is between 0.70 and 0.95, provided that
24 the scale is unidimensional. Regarding the number of subjects to include, rules-of-thumb vary
25 from four to 10 subjects per variable, with a minimum number of 100 subjects to ensure
26 stability of the variance-covariance matrix [34].
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34 **Floor and ceiling effects**

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36 Floor and ceiling effects will be determined by calculating the number of individuals who
37 obtained the lowest (floor) or highest (ceiling) possible scores and will be considered present
38 if more than 15% of the respondents achieved the lowest or highest score in a sample size of
39 at least 50 patients.
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44 **Construct validity**

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46 In order to evaluate the construct validity of DFU-FS and LEFS, we will use a set of
47 hypotheses between the instruments scores (convergent validity) and the population
48 characteristics or treatments (discriminative validity). In the literature, a positive rating for
49 construct validity is given if hypotheses are specified in advance and at least 75% of the
50 results are in correspondence with these hypotheses, in (sub) groups of at least 50 patients
51 [35]. Pearson's product-moment correlation coefficients (parametric data) or Spearman's r
52 (rank correlation) coefficients (non-parametric data) will be calculated. Correlation
53 coefficients above 0.6, between 0.6 and 0.3 and <0.3 will be considered high, moderate an
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3 low correlations, respectively. We will use Student's t-tests (parametric data) or Mann-
4 Whitney U tests (non-parametric data) to compare two groups of patients based on their
5 characteristics.
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9 We propose the following hypotheses:
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11 For the LEFS:

- 12 1. patients with bilateral foot lesions (ulcer and/or active Charcot and/or previous leg
13 amputation) demonstrate lower LEFS scores than patients with unilateral foot lesions.
- 14 2. patients with only plantar foot ulcers demonstrate lower LEFS scores than patients with
15 only non-plantar foot ulcers
- 16 3. patient with only toe wounds demonstrate higher LEFS scores than patients with wounds
17 at other locations of the foot.
- 18 4. there is a moderate negative correlation ($r=0.3-0.6$) between the LEFS score and the PEDIS
19 score of the most severe foot ulcer.
- 20 5. patients with bone involvement (PEDIS D3) demonstrate lower LEFS scores than patients
21 without bone involvement
- 22 6. patients with peripheral artery disease (PEDIS P2 and 3) demonstrate lower LEFS scores
23 than patients without peripheral artery disease (PEDIS P1)

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32 For the DFS-SF:

- 33 1. patients with bilateral foot lesions (ulcer and/or active Charcot and/or previous leg
34 amputation) demonstrate lower DFS-SF scores than patients with unilateral foot lesions.
 - 35 2. patients with only plantar foot ulcers demonstrate lower DFS-SF scores than patients with
36 only non-plantar foot ulcers.
 - 37 3. patient with only toe wounds demonstrate higher DFS-SF scores than patients with
38 wounds at other locations of the foot.
 - 39 4. there is a moderate negative correlation ($r=0.3-0.6$) between the DFS-SF score and the
40 PEDIS score of the most severe foot ulcer.
 - 41 5. patients with bone involvement (PEDIS D3) demonstrate lower DFS-SF scores than
42 patients without bone involvement
 - 43 6. patients with peripheral artery disease (PEDIS P2 and 3) demonstrate lower DFS-SF
44 scores than patients without peripheral artery disease (PEDIS P1)
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Criterion validity

Criterion validity refers to the extent to which scores on a particular instrument relate to a gold standard. EQ5D has been used in several pivotal studies in patients with DFU [36,37,38]. HRQoL scores will be measured at baseline and at 6 months (defined as 4 to 8 months). To evaluate the performance of DFS-SF, results of DFS-SF and EQ-5D will be correlated at the level of individual patients using Pearson or Spearman rank correlation techniques. In addition changes in the different domains of DFS-SF will be compared with changes in EQ-5D.

Responsiveness

Responsiveness is defined as the ability of a questionnaire to detect clinically important changes over time, even if these changes are small. The DFS-SF and LEFS questionnaires will be administered at baseline, at 6 months and at the moment of healing. Changes over time will be analyzed by calculating the differences between the three different time points for all questionnaire domains.

2.8 Sample size considerations

This study will test multiple hypotheses related to the following instruments: DFS-SF, LEFS and EQ-5D. Because the LEFS has not yet been used in the context of the diabetic foot, we cannot estimate sample size based on previously reported data using this instrument.

We estimated sample size at $\alpha = 0.05$ and power of at least 80%, as calculated by PROC POWER (SAS 9.4).

In the context of construct validity, we identified the following previously reported cross-sectional associations.

First, Kontodimopoulos et al. [38] reported associations of DFS-SF subscale scores with ulcer depth, graded as superficial, deep and up to bone. According to the group means and standard deviations reported by the authors, and assuming the ulcer depth distribution observed in IQED-Foot (14, 56, and 30% superficial, deep and up to bone respectively [7]), the estimated sample size is 100 patients for all subscales to detect a significant overall difference between the three groups with one-way ANOVA.

Second, Macioch et al. [39] reported Spearman rank correlation coefficients between DFS-SF subscales and PEDIS ulcer classification. The strongest correlation was between the

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3 “Dependence/daily life” subscale and PEDIS perfusion grade, with a correlation coefficient of
4 -0.312. The estimated sample size to obtain a similar correlation coefficient was 78 patients.
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6 Next, in the context of criterion validity (association of DFS-SF with EQ-5D), we identified
7
8 no publications to which we could compare to estimate sample size.
9

10 Finally, in the context of responsiveness we identified a number of publications reporting
11 mean and standard deviations both for DFS-SF and EQ-5D, but the follow-up was not always
12 6 months. We estimated sample size for a paired t-test according to 5 different scenarios,
13 depending on the extent to which within-patient scores were correlated over time: a
14 correlation of 0, 0.25, 0.50, 0.75 or 1.
15

16
17 Spanos et al. [40] reported the change in DFS-SF subscale scores after 12 months. The
18 estimated sample size range was 3-56 for the subscale with the lowest mean difference. The
19 highest sample size is that needed in the hypothetical case that a patients’ score was
20 completely uncorrelated between 0 and 12 months.
21

22
23 Holman et al. [41] reported the change in EQ-5D index score after 24 weeks. The estimated
24 sample size range was 3-177.
25

26
27 Li et al. [42] reported the change in EQ-5D index score after 12 weeks. We used data from the
28 control group. The estimated sample size range was 7-123.
29

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31 Siersma et al. [43] reported the change in EQ-5D index score after 12 months, separately for
32 patients whose DFU healed within 6 months of follow-up, after 6 months of follow-up or
33 whose DFU did not heal within 12 months. The estimated sample size range was 4-134, 3-
34 129, 3-720 for group 1, 2 and 3 respectively.
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37 In conclusion, a sample size of 100 patients seems sufficient to detect the most pronounced
38 cross-sectional associations reported in the literature, among the set of associations that we
39 are able to replicate in our study. With regard to the longitudinal change of HRQoL, there are
40 no studies on the DFS-SF using a 6-month follow-up. Based on the use of EQ-5D, we can
41 only compare to the study by Holman et al.: in the worst case scenario, the sample size needed
42 to detect a similar difference in HRQoL would be 177 patients. At a moderate within-patient
43 correlation of 0.5, the sample size needed would be only 90 patients, well within the
44 recruitment potential of the proposed study.
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54 55 **2.9 Patient and Public Involvement**

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58 It was not appropriate or possible to involve patients or the public in the design, or conduct, or
59 reporting, or dissemination of our research.
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3. ETHICS AND DISSEMINATION

Enrolment in this study does not have any influences on treatment. Verbal and written information including an information letter and an informed consent form will be given by a research physician or research nurses. Patients can always withdraw consent for inclusion of their data in the analysis.

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (2013), the principles of GCP and in accordance with all applicable regulatory requirements. This protocol and related documents were approved by the Medical Ethics Committee of OLV Aalst (Belgian registration number B126201836509). The Investigator and the Participating Site shall treat all information and data relating to the Study disclosed to Participating Site and/or Investigator in this Study as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the performance of the Study. The collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with General Data Protection Regulation (Directive 95/46/EC, Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement). The collected data will be coded. The clinical team will protect the data from disclosure outside the research.

The subject's name or other identifiers will be stored separately (site file) from their research data and replaced with a unique code to create a new identity for the subject. The research team will only have access to the coded research data.

The results of the study will be disseminated through peer-reviewed publications and conference presentations. If available at the time of publication, the results will be reported in accordance with the COSMIN Reporting checklist, which is a checklist that is still under development and will provide reporting guidelines for studies on measurement properties of PROMs [44].

4. AUTHORS CONTRIBUTIONS

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3 WR and FN developed the study. WR will act as a principal investigator. WR, FML, KD, GM
4 and FN were involved in writing the study protocol. WR, FML, KD, GM and FN will be
5 involved in assessment of outcomes. FML and KD will perform statistical analysis of the
6 study data. WR and FN drafted the manuscript.
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10 11 12 **5. FUNDING STATEMENT**

13
14 This research received no specific grant from any funding agency in the public, commercial or
15 not-for-profit sectors'.
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18 19 20 **6. CONFLICTS OF INTERESTS**

21 The authors declare no financial support from any organisation for the submitted work.
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24 25 26 **7. DATA AVAILABILITY STATEMENT**

27 All data relevant to the study are included in the article.
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30 31 32 **8. REFERENCES**

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