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IDENTIFICATION OF VALID AND MULTIDIMENSIONAL QUALITY INDICATORS IN DIABETIC FOOT CARE, USEFUL TO STUDY QUALITY OF CARE IN DIABETIC FOOT CLINICS

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Do the best you can until you know better.
Then when you know better, do better.

Maya Angelou

SUMMARY

Diabetic foot ulcer (DFU) is a common and serious complication that affects the feet of people with diabetes. Incident ulceration leads to lower extremity amputation in 20% of people and is significantly associated with mortality. The condition has an important impact on patient health-related quality of life (HRQoL) and represents major healthcare consumption and high costs. Therefore, there is a global search by the medical community for systems of quality monitoring and evaluation of diabetic foot care to ensure the delivery of the best possible treatment and minimize the burden for the individual as well as for society. Nevertheless, delivering optimal quality diabetic foot care is challenging. The complex pathophysiology of DFU requires a multidisciplinary care setting where different healthcare providers (HCP) have to interact with each other across care lines, in an often-lengthy care process. International guidelines together with national quality improvement initiatives have been implemented to optimize diabetic foot care, with Belgium playing a pioneering role with the national audit-feedback initiative for Quality Improvement and Epidemiology in Multidisciplinary Diabetic Foot Clinics (IQED-Foot). In such a demanding care process, providing optimal care, tracking practice variations and aligning performance are equally arduous.

Quality monitoring is impossible without the use of quality indicators (QIs). As they create the basis for quality improvement, QIs must be developed with scientific rigor (valid and reliable), taking into account the availability of the necessary information for establishing the measure (feasible) and covering all aspects of care to provide a balanced and comprehensive picture of healthcare quality (multidimensional). The existing quality initiatives were structured around quality indicators that were established based on the literature available at that time and the opinion of important key leaders in the field. Although the currently used QIs within the context of national quality initiatives have produced valuable outputs, a standardized approach for developing QIs is still lacking. In fact, this has been a shortcoming of similar quality systems all around the world: they are based on expert opinion and literature but no formal development process has been provided. Moreover, the strategy to compare QIs properly between diabetic foot clinics (DFCs) still needs to be improved. A more structured and evidence-based approach would strengthen existing QIs and provide new information. This would, in turn, enhance the quality monitoring that currently takes place within specialized multidisciplinary diabetic foot services and facilitate the achievement of quality improvement.

Belgian diabetic foot experts decided, based on their clinical experience, to focus on certain processes and clinical outcomes of care. A complete summary of the available evidence has not been provided since the current QIs have been established, implying that some relevant indicators may be missing. Therefore, in chapter 3 of this thesis, a systematic and open-minded search for interventions that could be used as evidence-based process or structure indicators was conducted. We have demonstrated the ability to formulate a set of 42 candidate indicators based on evidence-based, independently of expert opinion. This resulted in several indicator topics not commonly covered for evaluating diabetic foot care.

By formulating QIs supported by scientific evidence, we provided candidate QIs that may be used for the monitoring of safety and effectiveness of care delivered in DFCs.

In many areas of healthcare, limited or inconclusive evidence makes the development of QIs challenging. Consensus methods can help to address these challenges. Therefore, in chapter 4, a multidisciplinary expert panel was asked to evaluate the 42 evidence-based candidate QIs, in accordance with the Research And Development/University of California Los Angeles (RAND/UCLA) consensus methodology. We reported the selection of a set of 17 evidence-based QIs that were judged logical and clinically appropriate for monitoring quality within DFCs.

Together, chapter 3 and 4 provided the standardized approach, which was missing for developing QIs which following testing, could be used within DFCs for the monitoring of quality of care.

So far, no HRQoL measures have been included in the Belgian nationwide quality improvement initiative. Therefore, we conducted a monocentric, observational cohort study to assess the reliability of HRQoL questionnaires, with the aim to allow future integration into quality improvement systems. In chapter 5, we conducted our assessment based on standards defined by the COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) group. We made two patient-reported outcome (PRO) questionnaires understandable and relevant to Belgian Dutch-speaking patients with DFU, and provided reliability parameters comparable to those observed in similar studies of other language versions. Our work constituted the first step in assessing the measurement properties for evaluating both emotional and physical functioning of patients with DFU.

To make fair comparisons across the different diabetic foot services, a risk-adjustment strategy should be developed to isolate components that relate to the medical care system from factors beyond their control. Therefore, in chapter 6, we built a multivariable risk-adjustment model by using a bottom-up approach based on a nationwide database and accurate statistical methods. We described a detailed methodology to internally validate risk-adjustment models, tailor risk classifications systems to local clinical settings and establish benchmark.

In conclusion, we provided a mixed-method approach that enables to identify QIs in more rigorous and transparent manner, to achieve fair comparison and to broaden the scope of DFU care monitoring. This methodology allowed the reinforcement of existing QIs, while also providing additional insights for improving quality monitoring within diabetic foot services and other healthcare pathways. This PhD dissertation is a continuum of the national quality initiative IQED-Foot, which should be improved on the basis our findings and may serve as starting point for the global improvement of quality monitoring of diabetic foot services.

CONTENTS

LIST OF ABBREVIATIONS

A	
ABI	Ankle-brachial index
AP	Apparent performance
B	
BP	Bootstrap performance
C	
CI	Confidence intervals
c-index	Harell's statistic
CKD	Chronic kidney disease
CLI	Critical limb ischemia
COSMIN	COnsensus-based Standards for the selection of health Measurement INstruments
CV	Cardiovascular
CVD	Cardiovascular diseases
D	
DFC	Diabetic foot clinic
DFCS	Diabetic foot clinics
DFS	Diabetic foot ulcer scale
DFS-SF	Diabetic foot ulcer scale - short form
DFU	Diabetic foot ulcer
DFUs	Diabetic foot ulcers
DI	Disagreement index
DR	Diabetic retinopathy
DSPN	Distal symmetric polyneuropathy
E	
EBM	Evidence-based medicine
EHR	Electronic health record
EQ5D-3L	EuroqoL group five dimensions - 3 level version
ESRD	End-stage renal disease
F	
FTP	Fast-track pathway
G	
GP	General practioners

H

HbA1c	Hemoglobin A1c
HBOT	Hyperbaric oxygen therapy
HCP	Healthcare providers
HRQoL	Health-related quality of life

I

ICC	Intraclass correlation coefficients
ICHOM	International Consortium for Health Outcomes Measurement
IDFCG	International Diabetic Foot Care Group
IDF	International Diabetes Federation
int$	International dollar
IOM	Institute of Medicine
IPR	Inter-percentil range
IPRAS	Inter-percentile range adjusted for symmetry
IQED-Foot	Initiative for Quality Improvement and Epidemiology in Multidisciplinary Diabetic Foot Clinics
IWGDF	International Working Group on the Diabetic Foot

J

JCR	Journal citation report

L

LDL	Low-density lipoprotein
LEA	Lower-extremity amputation
LEFS	Lower Extremity Functional Scale
LOA	Limits of agreement
LOPS	Loss of protective sensation

M

MDC	Minimal detectable change
Mesh	Medical Subject Headings

N

NAM	National Academy of Medicine
NDFA	National Diabetes Foot Care Audit
NIHDI	National Institute for Health and Disability Insurance
NPWT	Negative pressure wound therapy

O

OCEBM	Oxford Center for Evidence-Based Medicine
OECD	Organization Economic Co-operation and Development
OLV	Onze-Lieve-Vrouw

P

P4P	Pay-for-performance
PAD	Peripheral artery disease
PDSA	Plan-do-study-act
PREMs	Patient-reported experience measures
PRISMA	Preferred Reported Items for Systematic Reviews and Meta-analysis
PRO	Patient-reported outcome
PROMs	Patient-reported outcome measures
PROs	Patient-reported outcomes

Q

QA	Quality assurance
QIs	Quality indicators
QI	Quality indicator

R

RAND/UCLA	Research And Development/University of California Los Angeles
RCT	Randomized clinical trial

S

SD	Standard deviation
SEM	Standard error of measurement

T

T1D	Type 1 diabetes
T2D	Type 2 diabetes
TBI	Toe-brachial index
TCC	Total contact cast
TcPO2	Transcutaneous oxygen pressure
TP	Test performance
TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis

U

UK	United Kingdom
US	United States
USD	United States Dollar

W

WHO	World Health Organization

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Chapter 1

INTRODUCTION

1.1 Diabetes mellitus

1.1.1 Prevalence

Diabetes mellitus is a chronic metabolic disease that is currently the eighth leading cause of disease burden in the world and the fastest growing one.[1] According to the International Diabetes Federation (IDF), the estimated prevalence of diabetes in people aged between 20-79 years was globally 10.5% (536.6 million people) in 2021, with a projected increase to 12.2% in 2045.[2] Estimates of diabetes prevalence based on the World Bank's gross national income classification were also provided. Diabetes prevalence has so far been demonstrated highest in high-income countries, with a prevalence of 11.1% compared to 10.8% and 5.5% in middle- and low-income countries respectively, but this is expected to change with the greatest relative increase anticipated for the middle-income countries. Yet, recent global issues like the COVID-19 pandemic, wars, and climate change make future projections of population body weight, obesity, and diabetes incidence less certain.[3] In Europe, about 9% of adults have diabetes.[4] Over the course of ten years, the Belgian prevalence has increased from 5.6% in 2012 to 7.1% in 2022.[5] Individuals with lower income, defined as beneficiaries from social aid (11.1%) are twice as likely to suffer from diabetes than those with higher income (6.1%).[5] However, national surveys showed that one in three people with diabetes are not aware of their diabetes, which suggests that the true Belgian prevalence of diabetes is likely to be around 10%.[6]

1.1.2 Pathogenesis

The majority of diabetes cases can be classified into two main etiopathogenetic categories.[4,7] Type 2 diabetes (T2D), which affects the majority of people worldwide, accounts for over 90% of all diabetes cases. This form, previously referred to as "non-insulin-dependent diabetes", encompasses individuals who have a non-autoimmune progressive loss of adequate beta cell insulin secretion on the background of insulin resistance and metabolic syndrome. Type 1 diabetes (T1D), formerly known as "insulin-dependent diabetes", is responsible for 5-10% of all cases of diabetes and is a distinct disease caused by the autoimmune destruction of beta cells, usually leading to absolute insulin deficiency. Given that both diseases can occur in adult and young groups, T2D and T1D should no longer be exclusively regarded as adult and juvenile diabetes, respectively. The typical clinical presentation of T1D is characterized by excessive thirst (polydipsia), frequent urination (polyuria), weight loss, and ketone production. Symptoms in T2D are usually much less pronounced or even completely absent. It may take several years before the diagnosis is made due to the difficulty of identifying early symptoms, which consequently results in a large portion of the population being unaware of their diabetes status. Regardless of the type of diabetes, the ultimate result is an increased concentration of blood glucose (hyperglycaemia).

The onset of hyperglycaemia places people, regardless of form of diabetes, at possible risk of developing chronic complications, although prevalence and rate of progression may differ according to factors such as the presence of metabolic syndrome (especially in T2D),[8] age at onset,[9] levels of hemoglobin A1c (HbA1c),[10] cardiovascular (CV) risk markers[11] and socio-economic status.[12] Compared to younger individuals, the vulnerable elderly population is exposed to a disproportionately increased risk of long-term complications due to the potentially longer diabetes duration attended with comorbid conditions and reduced functioning organ reserves.[9] Chronic complications are mainly consequences of damage to the macrovascular and microvascular functions and may appear as the first signs, leading to the diagnosis of diabetes if the latter has been unrecognized for a prolonged time.

1.1.3 Complications

Macrovascular diseases or cardiovascular diseases (CVD) represent the leading cause of both morbidity and mortality for people with diabetes. The types of CVD most commonly associated with diabetes are coronary heart disease, cerebrovascular disease, congestive heart failure, and peripheral artery disease (PAD), known as a significant contributor to lower extremity amputations (LEA). These conditions can manifest in the form of acute events, such as myocardial infarction or cerebrovascular accidents, but can also cause chronic problems, such as heart failure, claudication, and diabetic foot.[14] The presence of general cardiovascular determinants (e.g. elevated low-density lipoprotein (LDL), hypertension, and smoking), and factors that are more specific to diabetes (e.g. high HbA1c, and micro- and macroalbuminuria) contribute to a considerable extent to the elevated risk of CVD in individuals with diabetes compared with those without.[11]

The microvascular complications of diabetes include nephropathy, retinopathy and neuropathy. Chronic kidney disease (CKD) occurs in 20–40% of patients with diabetes and can lead to arterial hypertension, proteinuria, and/or a decrease in glomerular filtration rate. CKD typically develops after a 10-year duration of diabetes in T1D, but may already be present at the time of diagnosis of T2D. It can gradually evolve into end-stage renal disease (ESRD), a condition in which the kidneys are no longer functional, and that require dialysis or kidney transplantation for survival.[15,16]

Diabetic retinopathy (DR) is caused by microaneurysms and hemorrhages of retinal capillaries. Depending on the vascular damage in the retina, retinopathy can be characterized as non-proliferative (not vision-threatening), severe non-proliferative (vascular obstruction), proliferative (vision-threatening) and maculopathy (macular edema), making DR a leading causes of blindness. Risk factors associated with DR are diabetes duration, chronic hyperglycemia, CKD, hypertension, and dyslipidemia.[16,17]

Diabetic neuropathies represent the most prevalent chronic complication of diabetes, encompassing a heterogeneous group of disorders that affect different regions of the nervous system and manifest clinically in diverse ways.[18] The most studied forms of diabetic neuropathies are autonomic neuropathies and distal symmetric polyneuropathy (DSPN), known as peripheral neuropathy.

The former may affect organs such as sweat glands, resulting in a decrease in sweating and skin dryness that makes individuals vulnerable to skin lesions. The latter is the most widespread form in people with diabetes, accounting for approximately 75% of diabetic neuropathies.
DSPN has been reported to occur in at least 20% of people diagnosed with T1D after 20 years from the onset of the disease, while it may also be present in at least 10-15% of newly diagnosed patients with T2D, with rates reaching up to 50% after 10 years of disease duration. This chronic disorder is clinically defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes. The involvement of small fibers may result in pain and dysesthesias (unpleasant sensations of burning) whereas large fibers may cause numbness, tingling without pain, and loss of protective sensation (LOPS).
The damage of distal nerves of the limbs, particularly those of the feet, constitutes the most important cause of foot ulceration, and a prerequisite in the development of Charcot neuro-osteoarthropathy, also called Charcot foot. The occurrence of these late complications represents an important driver of amputation risks, health expenditure, and mortality.

Diabetes is a complex disorder that requires continuous medical care with multifactorial risk-reduction strategies beyond glycemic control. The disease and its associated complications represent a substantial burden for individuals and constitute a major public health issue as well. In European countries, the costs related to T2D range from 1.9 to 5.7% of total healthcare expenditure.[19] Therefore, implementing health strategies such as annual screenings, education programmes or quality-of-care improvement initiatives is critical for decreasing costs, optimizing care, and reducing long-term complications.

1.2 The diabetic foot ulcer complication

Diabetic foot disease is among the most serious complications of diabetes mellitus. The disease has several manifestations, with peripheral neuropathy (DSPN) and/or PAD playing a central role in its development. Among them, diabetes-related foot ulcer and Charcot foot are distinct conditions, but can be concomitant, and require complex management. Diabetic foot disease is acknowledged as a source of major social and economic burden for individuals and their relatives, HCP, and society in general.
In this PhD work, we focus on the diabetes-related foot ulcer.

1.2.1 Pathogenesis and classification of diabetic foot ulcers

A diabetic foot ulcer (DFU) is defined as a break of the skin of the foot that involves as a minimum the epidermis and part of the dermis in a person with current or previously diagnosed diabetes mellitus.[20]
The condition commonly results from diabetic sensory, motor, and autonomic neuropathy associated with mechanical stress. Sensory neuropathy leads to LOPS, motor neuropathy causes foot deformity and biomechanical abnormalities, while autonomic neuropathy leads to viscoelastic changes in the skin, such as skin dryness.[21]

These changes give rise to the development of very superficial or closed lesions that do not penetrate to the dermis (e.g., callous, blister, warmth, or erythema), and are indicative of a pre-ulcerative status (Figure 1.1).

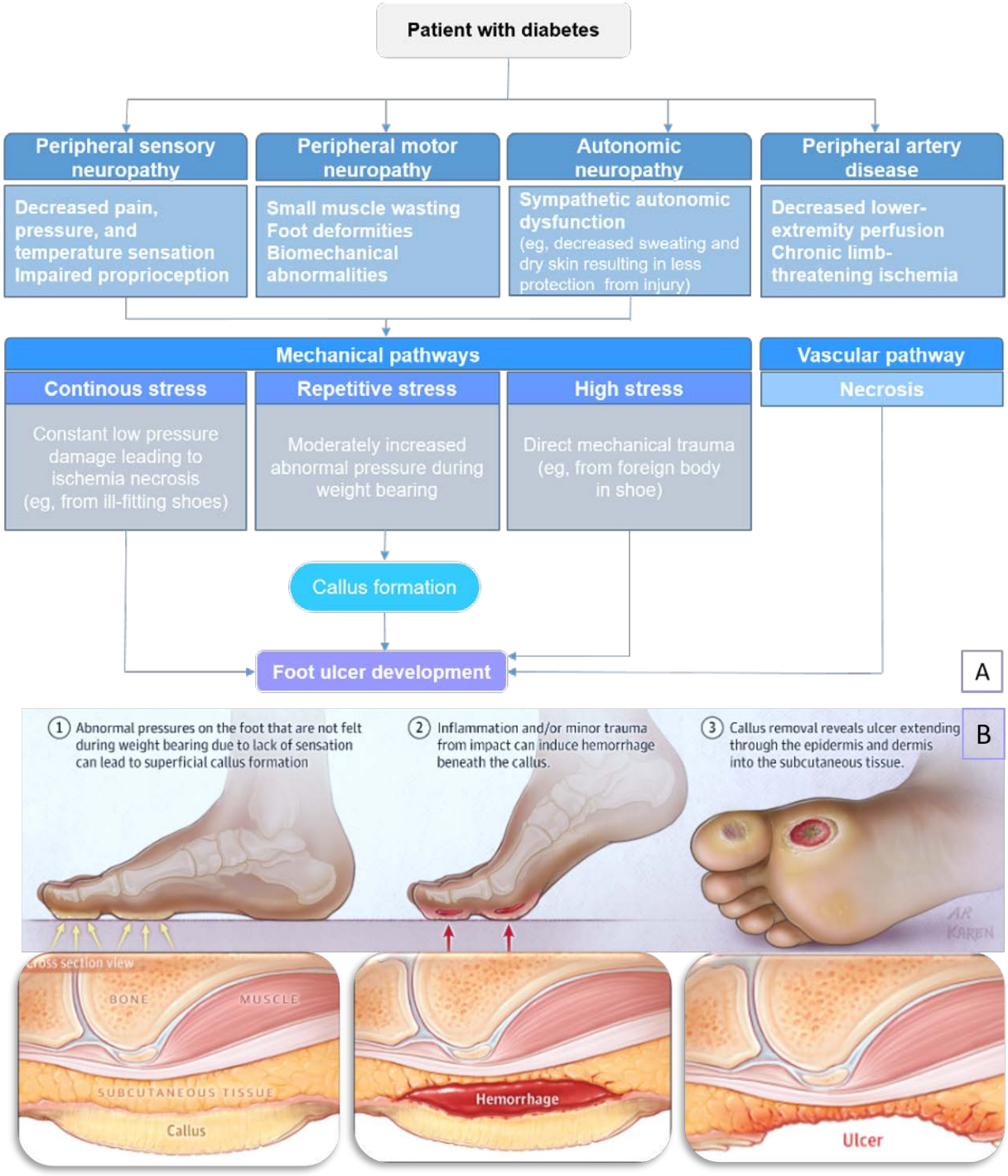

Figure 1.1. Pathogenesis of diabetic foot ulcers. Panel A shows the pathways to diabetic foot ulcer development. Panel B illustrates the development of a typical diabetic foot ulcer from mechanical stress. Adapted from Armstrong DG, Tan TW, Boulton AJM, Bus SA. Diabetic Foot Ulcers: A Review. JAMA. 2023 Jul 3;330(1):62-75.[21]

The resulting lesions can bleed beneath due to minor trauma and inflammation caused by the repetitive impact of the foot, particularly at elevated pressure at plantar weight-bearing sites or shearing stress, and present a full-thickness ulcer on its removal.[22,23] DFU can also develop as a result of constant low pressure, e.g., from tight shoes causing tissue necrosis, or extremely high pressure, such as a sharp object causing direct mechanical damage.[21] Because of the reduction of lower extremity perfusion, the presence of PAD is also associated with the development of foot ulcers.

Distinguishing between different types of ulcers is vital, especially concerning the presence or absence of peripheral neuropathy and associated sensory loss (neuropathic), PAD (ischemic), or both (neuro-ischemic). Classic neuropathic ulcers present as painless whereas purely ischemic ulcers are painful.[23,24] Neuro-ischemic or ischemic ulcers constituted 50-58% of all diabetic foot ulcers admitted to specialist care in large cohort studies conducted in Europe while plantar purely neuropathic foot ulcers made up 18-23% of all foot ulcers.[25,26] In contrast, the latter are much more frequent in regions of the Middle East and Africa.[27,28] In Belgian clinical practice, younger people present purely neuropathic ulcers more frequently, while elderly people develop neuro-ischemic more. The range and extent of tissue damage and wound characteristics in foot ulcers differ.[24] Classification systems aim to facilitate communication between HCP, assist clinical decision-making, help select patients for clinical trials, and evaluate the quality of care.[29,30] They were traditionally designed based on a “top-down” method, incorporating determinants that clinicians with experience in managing DFU deemed important. Several classification systems exist, including the Meggit-Wagner system[31], the PEDIS (Perfusion, Extent, Depth, Infection, Sensation) system[32], the SINBAD (Site, Ischemia, Neuropathy, Bacterial infection, Area, and Depth) system[33] and the University of Texas (UT) system[34].

1.2.2 Epidemiology and risk factors

According to recent reviews, the estimated global prevalence of DFU ranges from 18.6 million to as high as 33 million people worldwide.[35,36] The IDF even states that foot ulcers develop in 40 to 60 million persons with diabetes globally.[23] The prevalence and incidence estimates of DFU are subject to variation. This is attributable to differences in DFU definition, the registration completeness, and the selection procedures applied to identify people with diabetes in databases.[37] Furthermore, the estimates of DFU vary depending on the region of the world.[38] In Africa, the prevalence of DFU ranges from 10.0% to 30.0%. Conversely, the proportion of people with DFU in the South-East Asia region is typically below 15.0%. In the Middle East and North Africa countries, the DFU prevalence varies mostly between 5.0% and 20.0%. In North America, a prevalence of 13% has been reported.[36] In Europe, the prevalence of DFU has been estimated to be 5.1%. Among people with T1D or T2D, the lifetime risk of developing a foot ulcer has been estimated at up to 34%.[22] The condition is associated with high morbidity. About 50% of DFU become infected, which is the usual immediate precipitating factor for non-traumatic LEA.[21] Recurrence rates up to 65% at 3-5 years[22] and a lifetime LEA incidence of 19% have been reported,[39] leading to a burden for hospital admissions.[40]

Various factors contribute to the risk of foot ulcers in people with diabetes and can influence the outcome. These determinants can be related to patient or ulcer characteristics and can be (partially) described using the aforementioned classification systems. Among ulcer characteristics, several studies have reported that ulcer location, ulcer surface area, and vascular supply to the foot are strong determinants of DFU healing. Moreover, the presence of additional diabetes-related complications was found to be associated with DFU. Whilst PAD plays a direct role in the pathway to foot ulceration, other CV conditions, including congestive heart failure, coronary artery disease, and stroke are the common causes of death among people with DFU.[23]

ESRD and CKD are associated with an increased risk of foot ulcerations, longer healing times, higher ulcer recurrence rates, and a greater likelihood of LEA.[23,41,42]

Regarding patient characteristics, sociodemographic factors have been investigated. It is established that the risk of DFU is positively correlated with an individual's age; this is closely linked to a longer duration of diabetes, the cumulative effects of hyperglycaemia, and a greater prevalence of micro- and macrovascular complications.[23] A recent study revealed that men presented with more severe DFU than women and that female sex was a significant predictor of ulcer healing.[43] In addition, geographical and socio-economic disparities, resulting in differential access to appropriate healthcare services care,[44,45] social deprivation,[46] and financial restrictions that delay presentation,[47] contribute to worse DFU outcomes. Risk factors may also vary depending on the cultural environment. For instance, in sub-Saharan Africa, bare-foot walking and rodent bites on feet are associated with both occurrence and severity of DFU.[48] A further significant risk factor for adverse clinical outcomes is referral delay. Literature has shown that delay in care, including early management of a DFU, increases poor healing, infection, hospitalization, and LEA.[49] Presentation delay often results from a lack of education and knowledge about foot ulcers among both patients and HCP. Previous research has shown that general practioners (GP) often have poor instruction in the management of the diabetic foot and regular foot examinations in diabetic patients are uncommon.[50] Around the world, delayed referral of persons with DFU to specialised diabetic foot services remains a perennial concern.

1.2.3 Morbidity/Mortality related to DFU

Healing and recurrence. Ulcer healing can be considered the preferable outcome because it reflects the principal aims of DFU care, namely the return to normal function and limb salvage.[51] According to international guidelines, a healed foot ulcer is defined as the intact skin at a previous foot ulcer site, meaning complete epithelialization without any drainage.[20] Within 12 months of follow-up of DFU care, it is estimated that about 30 to 40% of DFUs heal.[21] Several patient, comorbidity, limb, and ulcer factors are associated with median healing times spanning from 3 months to more than 24 months.[52,53] Recurrence is the occurrence of a new ulcer in a person with DFU history, irrespective of the location and time since the previous foot ulcer.[20] Based on a previous review, recurrence rates were estimated to be around 40%, 60% and 65%, within 1, 3 and 5 years after healing, respectively.[22] Factors that have a consistent association with recurrence are comparable to those identified for non-healing.[54]

Infection. Infection is a common reason for emergency department visits and hospital admissions. Infection can rapidly lead to loss of foot tissue, increasing the risk of amputation. Severe infection can be life-threatening, and can even necessitate urgent amputation as a means of achieving infection source control.[55,56]

Lower extremity amputation. A lifetime risk of LEA of approximately 19% has recently been estimated in individuals with DFU.[39] While global databases demonstrate an incidence of LEA that seemed to decrease[38], some countries, including the United States (US),[57] Canada,[58] and England[59] no longer showed signs of decline with amputation, and even an increase for the US.[60]
In contrast, a significant decrease in the incidence rate of major LEA was observed in people with diabetes in Belgium from 2009 to 2018. Over the same time, the number of minor LEAs stabilized in the population with diabetes.[61,62] This probably reflects the impact of the implementation of more standardized and structured diabetes foot care, with the introduction of recognized DFCs in Belgium[63], and the good accessibility to Belgian healthcare.

Mortality. The 10-year risk of death is twice as high for a person with diabetes who has had a foot ulcer compared to a person who has not.[22] A previous study revealed that the 5-year mortality for people with DFU was 30.5%, which was comparable to the 5-year pooled mortality rate of 31.0% estimated from all reported cancer by American Cancer organizations.
Recently, a meta-analysis cumulating data from five different regions of the world found that death rates at 1, 3 and 10 years after incident DFUs were 86.9%, 66.9%, and 23.1%, respectively, with the leading causes of death being cardiovascular disease and infections.[64]

1.2.4 Impact on health-related quality of life

DFUs are a source of physical dysfunction, emotional distress, and overall, diminished HRQoL, described as a person's self-perceived impact of a medical condition, its symptoms, and its treatment on their physical, mental and social well-being.[65] People with DFU are subject to notable impairments in physical daily activities and social aspects of their life, such as limitations for climbing stairs or feeling tired all the time.[66] Reduced HRQoL, in terms of physical aspects and vitality, was also observed in people with a history of DFU, but it was still higher than in groups with active ulceration.[67] The presence of pain, poor physical health and social isolation can often lead to poor psychological well-being of the person with DFU. Several psychological factors, including fear of amputation, patient beliefs and depression are important in the context of DFU, and may hamper self-care behaviors.[68] Fear of amputation is emerging as a predominant emotion in DFU sufferers and may represent a powerful predictor of self-care behaviors.[69] People's awareness of their DFU condition is crucial because with high misperceptions about the nature of peripheral neuropathy, for example, they may undertake more often potentially damaging foot-care behaviors than those with generally realistic beliefs about the nature of DFU risks.[70,71]

A previous study found that people with diabetes having foot problems had, on average, significantly greater depression symptoms and elevated suicidal behavior than those without foot problems.[72] In addition, emotional difficulties were also observed in informal caregivers.[73] Given the detrimental impact of DFU on individuals with DFU and their relatives, it is crucial to measure aspects directly reported by the individual suffering from DFU, such as physical, mental, and social functioning.

1.2.5 Economic burden

Due to repeated hospital admissions and the risk of amputations, DFU generate considerable healthcare costs.[74] In the US, the cost related to diabetic foot care amounts to 9-13 billion USD in addition to the costs associated with diabetes itself.[75]

In Europe, the average total for direct (medical-related costs) and indirect (costs related to loss of productivity due to sickness leave) costs was approximately €10,000, based on prospective data from 14 European diabetic foot centres.[76] Indirect costs are likely underestimated, given the significant informal caregiving costs associated with diabetes and its complications.[77,78] Costs of treatment for a DFU classified as PEDIS extent grade 3 with LOPS, Wagner grade 1 (superficial), and UT low severity (grade 1, stage A) compared between Tanzania, India, Chile, China, and the US amounted to int$102, int$1,192, int$1,606, int$1,673, and int$3,959, respectively.[79] A previous review evaluated the economic aspects of diabetic foot care in a multidisciplinary setting.[80] They highlighted trends concerning excess costs, protraction in time of costs, positive correlation to severity of ulcer and/or peripheral vascular disease, contribution of in-hospital stay and length of stay, and the patient's contribution to total costs. In accordance with other economic studies on the problem of diabetic foot, a monocentric Belgian study, showed that the high cost of diabetic foot care was mainly attributed to costs of prolonged hospitalization and amputation, with an indirect and direct expenditure of USD10,572 per ulcer.[81]

More recently, a study found that amputation in individuals with diabetes was associated with high medical costs, reaching for major LEA up to €49,735 in the year preceding amputation and €45,740 in the post-amputation year[82].

1.2.6 Prevention and management of DFU

Prevention and management of diabetic foot complications is a centerpiece of diabetes care. Indeed, early recognition and treatment of patients with diabetes and feet at risk for ulcers and amputations can delay or prevent adverse outcomes.[16] Whilst a discussion of best-practice DFU care is beyond the scope of this PhD dissertation, it is important to give a short overview of the clinical practice that may be delivered by diabetic foot HCP. In this regard, the International Working Group on the Diabetic Foot (IWGDF) has been producing evidence-based guidelines on the prevention and management of diabetes-related foot disease since 1999.[83]

Prevention. Preventing foot ulcers in people with diabetes starts with timely detection and proper treatment of diabetes. Additionally, it is essential to identify who is most at risk of developing a foot ulcer.[84] This is achieved by evaluating the feet for neuropathy causing LOPS, for PAD, and for foot deformity or skin breakdown.

Based on this screening, people with the lowest foot ulcer risk, defined as people without LOPS, PAD, foot deformity, or history of foot complications, can be distinguished from people with diabetes who have an increased risk of foot ulceration. For the first group, an annual follow-up examination of the feet by a physician, diabetes nurse, or podiatrist is recommended.

For the second group, education on proper foot self-care and appropriate footwear, in addition to regular inspections and instructions on how to react in case of problems, should be provided.

Treatment of an active diabetic foot ulcer. The initial step is to classify the foot ulcer using one of the above mentioned classification systems that will guide the selection of an appropriate treatment strategy and facilitate communication between healthcare professionals.

Besides a systematic evaluation of the ulcer, the foot and the leg, it is also recommended to consider factors that may affect ulcer healing and treatment.[83] These include comorbidities, socio-economic and demographic status, and psychosocial factors, as previously highlighted. Depending on the clinical assessment that has been made, the treatment of a person presenting an active ulcer will involve different domains of interventions that should be used in conjunction. Local wound management consists in delivering interventions that enhance ulcer healing.[85] These encompass the removal of dead and devitalized tissue (sharp debridement), the selection of dressings to control excess exudation and maintain a moist environment, and when facing complicated wounds, the application of adjunctive treatments, like for instance, negative pressure wound therapy (NPWT). Offloading repetitive mechanical stress on the foot, achieved by reducing weight bearing on the ulcer, represents an important aspect of treatment and reduces pressure over the wound by redistributing the force over a larger unit area.[21,86] Treatment of PAD consists in performing lower extremity revascularization which aims to restore pulsatile arterial flow to the foot.[21,87] Treatment of infected DFU involves debridement, surgical intervention to remove deeper or more extensive necrotic and antibiotic therapy.[56]

Multidisciplinary care. A foot ulcer in a person with diabetes is a consequence of multifactorial pathology. Therefore, it is important to adopt if possible a multidisciplinary approach to address the diverse etiologies that synergistically contribute to lower-extremity ulceration, infection, and subsequent amputation.[88] A multidisciplinary team approach has been shown to reduce diabetes-related lower extremity amputation.[89] Generally, the composition involves at least 1 medical specialty clinician (most commonly endocrinology, infectious diseases, or primary care) and 2 or more surgical specialty clinicians (vascular, podiatric, orthopaedic, or plastic surgery). Nevertheless, the team composition and activities of a multidisciplinary team can vary.[90] The effectiveness of DFU care depends not only on the team but also on the organizational systems and guidelines for all aspects of standard care. As recommended in the IWGDF guidelines, diabetes-related foot care should cover different dimensions such as access to multidisciplinary care or the implementation of a structured organization and monitoring systems, which contribute to the delivery of qualitative care.[83]

Improving diabetic foot care is crucial since providing the best possible treatment to people with diabetes lowers the risk of developing DFU, associated comorbidities, and mortality risk, while it increases the quality of life and minimizes the use of healthcare resources.

1.3 Quality of care

1.3.1 What is quality of care?

Quality of healthcare or quality of care is a principle of health policy that has gained increasing attention over time and is currently high on the agenda of most global institutions and medical stakeholders.[91] Depending on the purpose and the stakeholders involved, addressing the issue of healthcare quality may be motivated by different reasons, including, for example, the belief that access to high-quality care is a fundamental human right, the concerns about substantial practice variations in standards of healthcare delivery, the recognition of the need to align the performance of collaborating HCP, and the detection of gaps in safe, effective and person-centered care.

The quality movement took root in healthcare with the work of different public health figures.[92] In the classical period, Hippocrate, the Father of Medicine, issued principles that remind physicians of their obligations to act solely for the benefit of their patient and to refrain from causing harm.[93] More than two millenniums later, his doctrine remains relevant and has been complemented by the contributions of other healthcare professionals committed to making changes. In 1847, Ignaz Semmelweis initiated hand washing policy in hospitals for infection control that would improve patient safety.[94] Thereafter, Florence Nightingale carried out a remarkable hospital quality improvement project by documenting processes and outcomes of care in 1855.[95] Fifteen years later, Ernest Codman pioneered the concept of standards in healthcare.[96] In the latter half of the 20th century, healthcare adopted quality improvement concepts that originated from the manufacturing sector, where it was initially mainly used.[97] The approaches of individuals such as Shewhart (*Statistical quality control, Plan-Do-Check-Act cycle*), Juran and Deming (*Theory of improvement*) contributed to the foundations for qualitative healthcare.[98] Later in the 1970s, the quality movement gained strength with the visionary perspectives of Archie Cochrane and David Sackett, who established the fundamental principles of evidence-based medicine.[99,100]

The quality of care definition has been evolving over the years and across contexts. The pioneering definitions, and still most influential, have been provided by Donabedian in 1980 and by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), in 1990. Avedis Donabedian defined quality in general terms as *the ability to achieve desirable objectives using legitimate means*.[101] In his attempt to define and measure quality, he advocated for the need to assess healthcare into three aspects, i.e. structure, processes and outcome measures.[102]

Structure denotes *the attributes of the settings in which the care occurs*. *Process* refers to *what is actually done in giving and receiving care*. *Outcome* denotes *the effects of care on the health status of patients and population*. A decade later, the IOM study committee brought together a set of key parameters and defined quality of care as follows: *the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowled*ge.[103] Subsequently, the same organization outlined six major aims, or domains for healthcare that are deemed necessary to pursue: healthcare should be safe, effective, person-centered, timely, efficient and equitable.[104] It is important to note that some modifications have been implemented so far, with the use of "person-centered" instead of "patient-centered" and the inclusion of "accessibility" and "affordability" to expand the dimension of timeliness.[105]

To date, the Donabedian and IOM definitions and domains have formed the basis of efforts for addressing quality of care. In addition to these quality frameworks, further dimensions that expand the scope of quality of care have been proposed. The domain of integrated care was introduced by the European Commission and the World Health Organization (WHO).[91]
The International Consortium for Health Outcomes Measurement (ICHOM), led by Michael Porter, proposed a more comprehensive focus on the dimension of outcome for achieving high value for patients, defined as the health outcomes achieved per dollar spent.[106] Recently, a new multidimensional quality model has been produced by senior contributors in quality thinking.[107] In light of new societal challenges, Lachman, Batalden and Vanhaecht rethought the six IOM dimensions by proposing new domains such as ecology and transparency and the change of person- to 'kin-centred care'. This switch draws attention to relationship as fundamental and embraces the shared humanity of patients, their relatives and HCP involved in the interdependent work of healthcare. The new model contributes to transferring power to the person rather than remaining in the system and facilitates the achievement of equity in healthcare.

While the definitions put forth by Donabedian and IOM are widely disseminated, it is also important to consider the relationship between evidence-based medicine (EBM) and quality of care. It is commonly accepted that EBM will improve the quality of care. According to David Sackett, EBM can be defined as "*the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients, which integrates the best (external) evidence, i.e. clinically relevant research, with individual clinical expertise and patient's choice".*[108] In accordance with Sackett's definition, EBM promises quality of care. EBM and quality of care share common characteristics of quality of evidence, duty of care, and patient choice and involvement.[109] However, EBM should be practiced to improve quality of care while considering complex interactions. For instance, although medical practice may quickly become outdated and detrimental to patients without current best evidence from scientific research, evidence should never fully replace individual clinical expertise, as it is this expertise that decides whether the external evidence applies to the individual patient at all and, if so, how it should be integrated into a clinical decision.[108] Moreover, real tensions may appear between clinical judgement, personal knowledge of the patient and guideline recommendations.

The use of EBM by physicians should be seen as a means of justifying their actions based on evidence, which would circumvent the paternalism often associated with the authority of medicine.[109,110]

Because quality of care has become a top priority across the world, researchers, policymakers and HCP have been increasingly seeking to develop and implement strategies for understanding, assessing and ultimately improving the quality of healthcare.[111] Quality strategies can be implemented at different levels where processes contributing to quality may take place,[102] although various definitions of levels have been conceptualized. In its reviews of healthcare quality, the Organization Economic Co-operation and Development (OECD) grouped quality strategies into system level, institutional/organizational level and patient/community level.[91,112] According to this categorization, strategies have been listed based on Slawomirksi, Auraaen & Klazingan,[113] and WHO[114] contributions.[91] Examples of system level strategies are regulation and licensing of provider organizations/institutions, public reporting and comparative benchmarking, pay-for-performance (P4P) initiatives, electronic health record (EHR) systems. Organizational/institutional level strategies could be clinical guidelines, clinical audit and feedback, and collaborative or team-based improvement cycles. Examples of patient/community level interventions include peer support and expert patient groups or monitoring of patient experience of care.

Measuring quality of care is a cornerstone of many quality strategies. In fact, national policy-makers acknowledge that without measurement tools for documenting, benchmarking, making judgments and setting priorities, it is difficult to ensure high-quality of healthcare provision in a country.[111,115] Quality measurement can be driven by two main purposes and involves many potential users of quality information.[111,116] The first purpose is for summative use, which provides a structured way to demonstrate that a range of key objectives (in this case, indicators) have been met and to receive useful feedback on their overall performance. This has the purpose to increase the external accountability of hospitals towards different stakeholders (such as government, patients or health insurers), also called quality assurance (QA). Measurement for QA focuses on identifying and overcoming problems with quality of care and assuring a sufficient level of quality across HCP. This may be pursued, for example, through P4P initiatives or licensing of providers based on external assessment. The request may arise from governments and regulators. Quality information could also be distributed through public reporting and used by patients and citizens. In this way, patients are assured that adequate health services and providers of good-quality care are available.

The second is for formative (internal) purposes by health care organizations and providers to measure, monitor and improve the provided levels of quality of care, also known as quality improvement. Quality information is used at the local level by care professionals (HCP, researchers, and administrators) and monitored for instance across an audit and feedback system, to promote continuous efforts, monitor deviations from scientific standards or benchmarks and improve performance. Furthermore, the quality measurement has to differ depending on whether the quality is measured in the preventive, acute, chronic or palliative care setting because the goals and the speed of the impact on health outcomes (e.g. slow in preventive, fast in acute care) are different. To achieve those purposes, quality strategies must rely on reliable and valid quality indicators.[117]

1.3.2 Quality indicator: the key tool for assessing quality of care

Definitions, sources and types

A quality indicator of care (QI) is defined as a measurable aspect of care (structure, process or outcome) for which there is sufficient evidence and/or consensus that it can be used to evaluate quality of care and its evolution.[102,118] In other words, QIs describe the performance that should occur for a particular type of patient or the related health outcomes, followed by the assessment of whether patients' care is consistent with the indicators based on evidence-based standards of care. The use of indicators allows healthcare professionals and organizations to monitor and evaluate what happens to individuals with a condition as a result of the functioning of professionals and organizational systems function to meet the needs of affected people.[117] Indicators are however not quality *per se*, but rather a means of assessing the dimensions considered critical to quality.[119]

There are different sources of QIs, including administrative data, medical records, disease-specific registries, survey data and direct observations.[111] The most commonly used are administrative data, medical records, and disease-specific registries. Surveys help gain insight into patient or HCP perspectives, and thus into particular dimensions of quality. Direct observations such as visits between peers (peer visits), may be useful for continuous quality measurement when coupled with data from administration, medical records or disease-specific registries, to investigate unexplained variations between HCP and to better understand the local context. In accordance with the quality purpose mentioned above, QIs may be used in a summative (QA) or formative perspective (quality improvement). QIs for QA should enable to make summative judgements about the quality of care provided, and should demonstrate whether certain levels or objectives have been met, which means that "real" differences will be detected as a result of a quality initiative such as a P4P initiative or public reporting. Therefore, a high level of precision is necessary and advanced statistical techniques may need to be employed to make sure that detected differences between providers are "real" and attributable to provider performance. By contrast, QIs for formative perspectives do not necessarily need to be perfect because it is generally informative. The results of quality measurement can be used to start discussions about quality differences and to motivate change in provider behavior such as across an audit-feedback system.[111] QIs can combine formative and summative purposes.

QIs can be classified according to the different dimensions of quality mentioned above. The most commonly used framework for classifying indicators is the Donabedian's triad referring to the three aspects of healthcare: structure, process, and outcome.[102] This framework can be articulated across the different dimensions of quality provided by the IOM[104] and/or more recent quality frameworks.[106,107] In general, structure indicators describe the type and amount of material (e.g. facilities, equipment, and money) or human (e.g. the number and qualifications of personnel) resources used by a health system or organization to deliver care programmes and services, as well as attributes of organizational structure (such as medical staff organization, methods of peer review and methods of reimbursement).[102,117]

For example, structure indicators related to effectiveness include the availability of staff with appropriate skills.[111]

Process indicators assess the practitioner's activities in making a diagnosis, recommending or implementing treatment, and how well it was done, as well as other interactions with the patient.[102,117] A process indicator of effectiveness may assess the delivery of standard of care, while a process indicator related to person-centeredness may evaluate whether doctor provides easy-to-understand explanations to the patient.[111] Finally, outcome indicators measure states of health or events that follow care, and that may be affected by health care.[117] Examples of outcome indicators covering effectiveness include mortality, morbidity, or functional status. Outcome indicators of person-centeredness may assess patient satisfaction or willingness to recommend the hospital.[111]

Additionally, it is useful to make a distinction between rate-based and sentinel indicators.[117] A rate-based indicator uses data about events that are expected to occur with some frequency. These can be expressed as proportions or rates with a clearly defined denominator, i.e. the population evaluated by the indicator, and a numerator, i.e. the proportion of the denominator that satisfies the condition of the indicator. A sentinel indicator identifies individual events or phenomena that are intrinsically undesirable, and always trigger further analysis and investigation.

Given the growing emphasis on incorporating the patient's perspective in clinical settings, a closer examination of this topic is warranted. The health status or the experience of receiving healthcare from the patient's perspective can be captured by self-administered questionnaires, which are referred to as patient-reported measures. Patient-reported outcome measures (PROMs) provide the patient's perspective on their health status (e.g., symptoms, functioning, mental health); whereas patient-reported experience measures (PREMs) capture the patient's view on a health service delivery (e.g., communication with nurses and doctors, staff responsiveness, discharge and care coordination).[120] The OECD has stated that the collection and reporting of patient-reported experiences and outcomes can be used to monitor and inform HCP performance over time, and can help to gain new knowledge on how to improve lives for all, in view of promoting person-centered care.[121] To date, despite the widespread use of PROMs and PREMs, particularly in the context of chronic conditions, evidence about the real impact of patient-reported data is not conclusive yet, but promising. Prior to testing the implementation of patient-reported data monitoring, it is crucial to evaluate the measurement properties of patient-reported questionnaires.

Criteria for a good quality indicator

QI provide a quantitative basis for different stakeholders aiming to achieve standards of care and improvements in care. Therefore, prerequisites should be established. Five broad criteria for developing good indicators have been defined by the IOM. These include importance, scientific soundness, feasibility, alignment, and comprehensiveness.[122,123] The criterion of importance refers to the impact on health. A QI must address health problems that are at the forefront of different stakeholders' attention and must be susceptible to change (actionable). The scientific soundness of an indicator is reflected by its reliability and its validity.

Reliability means that the indicator consistently produces the same result when repeated within the same population and setting, implying the availability of reliable data sources and the statistical reliability of the indicator (sample size power, measurement error, risk-adjustment).

The reliability should be tested to ensure that the QI is measured using data sources that accurate enough to provide reproducible results. The validity of an indicator refers to the degree to which an indicator measures what it is intended to measure. The concept of validity encompasses several dimensions, including content and face validity, reflecting whether the indicator is derived from evidence (content) or formal consensus (face), criterion validity, and construct validity. Criterion validity refers to the idea that the indicator should be closely related to other measures of the same construct, and is composed of 2 forms, including concurrent validity (comparison with existing measures assessing the same construct) and predictive validity (able to make accurate predictions about the construct).[124] Construct validity reflects how well the indicator measures theoretical constructs. The feasibility of an indicator concerns the data needed for establishing the measure; they must be reliably available and examined for the cost or burden of measurement on providers. Indicators should be maximally aligned with existing indicators and standards, and their definition should remain within the same technical specifications for both the numerator and denominator, considering updates as evidence evolves. The comprehensiveness of an indicator set involves measuring all aspects of care to provide a balanced and comprehensive picture of healthcare quality.

Conceptual approaches for developing a quality indicator

To meet the criteria for good indicators, QI must be developed, tested and implemented with scientific rigor, which implies following methodological key steps.[115,125] A literature review should be conducted to search for scientific evidence to underpin the QI, and so ensure content validity; the stronger the evidence, the stronger the rationale and potential benefit of the indicator. There are many types of reviews depending on the purpose, including systematic review, topical review, narrative review, etc. More recently, evidence synthesis has seen the emergence of scoping reviews.[126] Similarly to systematic reviews, these reviews require a structured, rigorous and transparent process to ensure trustworthy results. Scoping reviews are conducted instead of systematic reviews when the purpose is to identify available evidence and knowledge gaps in a given field.

However, the identification of available evidence for defining QIs in many areas of healthcare is challenged by limited or inconclusive scientific evidence or lack of evidence for the specific population of interest, requiring the extrapolation of results from other patient populations.[125,127] These challenges can largely be addressed with the use of a consensus method, which constitutes the most common formal approach to making decisions, generating ideas or establishing a ranking when scientific evidence is inconclusive, conferring face validity to a QI. It is based on the involvement of a group of stakeholders, who discuss the topic taking into account different perspectives and providing a more nuanced input, considering clinical relevance and feasibility.[127,128] Several consensus methods exist, including the consensus development conference, the Delphi method, the nominal group method, and the RAND/UCLA Appropriateness Method.[128]

Among them, the RAND/UCLA method is the single approach that incorporates a quantitative rating of the feasibility of collecting data.[129] In addition, unlike the Delphi or the nominal groups method, its validity has been investigated in the healthcare domain.[130,131]
Scientific literature and/or stakeholder formal consensus provide evidence about a linkage between any particular component of structure or process used to define a given QI and an outcome, reflecting the validity of the indicator. In other words, for a structure or process indicator to be valid, it must previously have been demonstrated to produce better outcome.[117]

While identifying QIs, a risk-adjustment strategy should be defined to ensure that variables outside the control of HCP do not influence comparisons of indicators across hospitals and providers. Risk-adjustment consists of controlling for significant confounding factors[132], and is most important for outcome indicators because variations in outcomes should be attributable to variations in the quality of care. The determination of a risk-adjustment approach requires two main elements: the identification of prognostic factors (patient characteristics, sociodemographic factors, severity of the illness, health status, and co-morbid conditions) and the use of appropriate statistical techniques.

The development phase must be followed by steps in which the measures will be subject of testing. Indeed, a real EBM approach of the use of QI implies an intervention study in which the use of the QI (or a set of QIs) is the intervention itself. Although each QI may be described in details, preliminary testing may identify areas requiring further modifications, thus allowing the feasibility of implementation to be tested. In addition, it may help to test the complementarity with existing QIs.

As stated earlier, quality of care has become a top priority for most healthcare systems. This is particularly true in the world of diabetic foot, and more specifically in the Belgian healthcare community.

1.4 Quality of care in diabetic foot

Multidisciplinary approach: cornerstone of quality of care in diabetic foot

Improving quality in diabetic foot care is currently an important goal for the multiple stakeholders involved, particularly given the major burden of DFU[35,36] as well as the huge impact on quality of life[66,67,72] and healthcare expenditure.[74,81,82] However, the multifactorial pathophysiology of DFU makes its understanding and management complex. To tackle this complexity, better collaboration between the various specialties involved in diabetic foot care is recommended, which leads to greater efficiency and sets the basis for higher quality of care.
The history of team approach in DFU care started in the US with pioneers like Maurice Lewi in 1911 and later, Elliot Joslin in 1934.

Joslin was the first to assert that a team approach that included foot care, diet, exercise, prompt treatment of foot infections, and specialized surgical care, was the remedy to the diabetic gangrene of the lower extremity.

Subsequently, several milestones and system changes involving different figures and teams occurred in the US that contributed to the landscape of management of the diabetic foot. Furthermore, in the mid-20th century, the work of figures such as Paul Brand, who transposed his work on leprosy patients to patients with DFU, contributed to the understanding of the pathogenesis of neuropathic foot lesions in diabetes and shaped diabetic foot care until the present day.[133]

At the same time, the notion of multidisciplinary care spread around the world. [134]

In the African continent, many efforts have been made by Abbas *et al*. who involve nurses and other personnel in all aspects of foot care.[135]

In Europe, the introduction of a multidisciplinary approach for treating people with DFU can be traced back to the 1980s, with the first DFC established in the United Kingdom (UK) by Michael Edmonds in the Podiatry Department of King's College Hospital in 1981.[136] Afterwards, different multidisciplinary DFCs were set up in Europe.[134] William Jeffcoate instituted a multidisciplinary clinic in Nottingham in 1982 while Andrew Boulton established one in Manchester in 1987. In 1983, Jan Apelqvist was appointed director of a multidisciplinary clinic in Sweden. In 1984, Max Spraul and Ernst Chantelau initiated a DFC in Dusseldorf. During the 1980s, Ezio Faglia published about work performed in a multidisciplinary centre in Italy. Later, work from DFCs in the Netherlands was also reported.[137] In Belgium, the diabetologist Kristien van Acker launched the first DFC at the University of Antwerp in 1989. The clinic started with two nurses and a podiatrist and was later on, organized according to the model of Andrew Boulton. A large multidisciplinary team was in place over the course of the following 14 years. Concurrently and independently of each other, DFCs were initiated at the academic hospital of Catholic University of Louvain (UCLouvain Brussel) by Bernard Vandeleene, and thereafter at the Onze-Lieve-Vrouw (OLV) Aalst Hospital by Frank Nobels.[63]

Initiatives to support the Multidisciplinary approach.

In October 1989, representatives from government health departments, patient organizations, and diabetes experts from various European countries convened to establish goals and objectives for improving global diabetic foot care under the leadership of WHO and the International Diabetes Federation (IDF).[134,138] The resulting Declaration of St Vincent set amongst others aims for diabetic foot care by encouraging the development of multidisciplinary clinics and providing a target for reducing the rate of LEA for diabetic gangrene by as much as 50% within 5 years.[139] A decade later, an international set of definitions and guidelines on prevention and management of diabetic foot, was designed to support multidisciplinary teams worldwide by the freshly formed International Working Group on the Diabetic Foot. So far, the IWGDF has provided practical guidelines on the organization of diabetic foot care in a cycle of four years.

Variations in diabetic foot care

Despite the existence of international guidelines to support multidisciplinary teams, high variability has been observed between geographical areas. Amputation rates were for example seen to vary greatly between and within countries.[137,140,141] Additional evidence showed marked differences in management in terms of referral to foot clinics, use of offloading and vascular assessments between 14 centres across European countries.[142] In the case of referral, large variations (6-55%) were observed, suggesting that in some areas there was much room for improvement. In addition to these inter-country differences, intra-country differences were also revealed. The existence of differences at the national level was later confirmed by Doggen *et al.*, which showed important variations in the delivery of interventions including offloading (64-100%) and revascularization (22-69%) between Belgian centres.[143]
In the literature, evidence converged to indicate that the observed variations in DFU management may be explained at least in part by variations in the clinical decisions made by HCP, suggesting a gap between recommendations and everyday clinical practice.[144,145]

The understanding, monitoring and reduction of variations contribute in improving quality of care and represent the fundamental principles of most quality improvement programmes using QIs.[119] Accreditation criteria and QA strategies have been implemented in Germany,[63] UK,[146] Italy[147] and Belgium,[143] to monitor variations and improve the quality of care delivered in diabetic foot services.

Quality measurement initiatives for diabetic foot services

National quality frameworks abroad. In Germany, a small group of physicians and surgeons called the German Working Group on the Diabetic Foot wrote a policy statement for amputation prevention. From there, building structures for implementing the underlined clinical points became a principal priority.
In that context, the group developed a certification for diabetic foot services at the national level in 2003. The certification relies on QIs related to structure, process and outcome of care used for benchmarking and allowing specialized centres to monitor the quality of their management. Each centre documented 30 consecutively seen individuals with diabetic foot lesions, with a follow-up of outcome up to 6 months after the initial presentation. The accuracy of the provided information by the applicant centres is controlled through mutual auditing visits between the centres, leading to a certification for 3 years.[63,148]
In the UK, a government commitment in 2001 was released to improve diabetes care. From that initiative, a national working group was established in England and Wales to consider measures for the assessment of different aspects of the pathway of care for disease of the foot in diabetes. The National Diabetes Foot Care Audits (NDFA) were launched in 2014 and focused on indicators related to diabetes management, ulcer outcomes at 1 year, but also patient-reported outcomes measures.
The output is a national report that identifies important trends in foot care processes and outcomes, enabling HCP to measure their performance against clinical guidelines and peer units.[146,149,150]

In Italy, following a retrospective study that evaluated the prevalence and incidence of foot lesions requiring hospitalizations, a regional diabetic foot programme was set up in the region of Tuscany from 1999 onwards.[147]

As in the aforementioned quality initiatives, indicators related to diabetes management and ulcer outcomes are being collected. The programme is based on a P4P model that rewards centres financially based on the performance they achieve.

Belgian quality framework. The implementation of quality programmes for diabetic foot care in Belgium started in 1992 with the creation of "The Belgian Task Force" for better diabetes care, as a result of the St Vincent Declaration. In 1998, the working group "Prevention and Treatment of Diabetic Foot, compounded of Van Acker and Vandeleene started the Belgian implementation of a screening programme to obtain an overview of the presentation of diabetic foot lesions, the amputation rate and the prevalence of patients with a foot at risk.[138] Two years later, Van Acker and Nobels started the next phase of the programme with an interactive education module on diabetic foot for primary HCP. From that point onwards, it became evident that more structured care with well-organized DFCs was mandatory.[63] Consequently, in 2005, the quality improvement initiative IQED-Foot was implemented, inspired by a similar project established four years earlier in over 100 Belgian hospital-based diabetes centres and aiming to improve adherence to diabetes care guidelines.[143]

The IQED-Foot initiative consists of audit-feedback cycles and anonymous benchmarking that involves several stakeholders, including the specialized multidisciplinary DFCs, a group of diabetic foot experts, the Belgian Institute of Public Health (Sciensano), and the National Institute for Health and Disability Insurance (NIHDI) (Appendix 1.1). DFCs can apply for recognition by NIHDI, which then provides funding (a small flat fee per patient) for the coordination and operation of the DFC. To be qualified, a DFC needs to treat at least 52 patients with diabetes and a new index 'foot problem' each year: either a severe DFU of Wagner grade 2 or more, or an active Charcot foot.[31] Further criteria for recognition are the minimal staffing of the multidisciplinary team (diabetologist, surgeon on call and immediately available, podiatrist, diabetes nurse, footwear technician), and the compulsory participation to a prospective data collection for quality improvement.[151]

Patient demographics and medical information are collected together with a series of indicators of processes and outcomes of care.[63] The process indicators are related to the following interventions: wound care, offloading, vascular diagnostics, revascularization, orthopaedic surgery, podiatric interventions and secondary prevention (Appendix 1.2). The outcome indicators include ulcer healing, relapse or new ulcers, major amputation and death (Appendix 1.2). Data are collected using a standardized electronic questionnaire via the HealthData.be platform. The variables collected are defined by a committee of experts consisting of HCP from the participating DFCs, a representative of NIHDI and researchers from Sciensano.[151] After completion of the 6 months of follow-up, DFCs transfer the data to Sciensano, for data quality checks, analysis and generation of feedback reports.[143]

The multiple outputs from IQED-Foot contribute to an improvement in quality of diabetic foot care.[143] Two types of feedback reports are generated at the end of each cycle; an individualized feedback report with anonymous benchmarking for each recognized DFCs and a global report based on the aggregated national results, which is available for health authorities and the general public.

The individual feedback reports show the process and outcome indicators collected from the recognized DFCs in the form of descriptive tables and graphs, which allow anonymous comparisons and identification of areas for improvement. Furthermore, these reports can serve as the basis for implementing a local PDSA (Plan-Do-Study-Act) cycle, which ensures continuous improvement of the processes and encourages a culture of learning, experimentation and adaptability. In addition, the national results are discussed during a biannual information meeting open to all recognized DFCs and their team members. These meetings allow to increase awareness of specific issues, to improve knowledge among DFC team members, and to discuss among peers and exchange experiences. In addition to the information meetings held within IQED-Foot, the recognized DFCs, in collaboration with Sciensano and patient organizations, organize further regular symposia, focusing on specific processes of care or identified gaps in delivery of care. Recently, peer visits have been organized, during which recognized DFCs can exchange on best practices in the organization of care and treatment of DFU, with the ultimate aim of improving the quality of care and reducing the variation in practice between DFCs.

Chapter 2

RESEARCH OBJECTIVES

2.1 Rationale for undertaking the research

Diabetic foot disease is among the most serious complications of diabetes mellitus. The condition and its associated manifestations represent a major health, social, and economic burden for individuals and their relatives, care providers, and society in general. Therefore, delivering appropriate diabetic foot care is crucial since delivering the best possible treatment to people with diabetes lowers the risk of developing DFU, its associated comorbidities and mortality, increases quality-of-life and minimizes the use of healthcare resources. Nevertheless, providing optimal quality diabetic foot care is challenging. This is due to the complexity of diabetic foot prevention and care, and the diverse presentations of DFU, with large variations in severity and dimensions of the problem and a large impact on the quality-of-life of patients. In addition, the involvement of multiple HCP within a single diabetic foot service, as well as across care lines, each with their different expertise and backgrounds adds another layer of complexity. In parallel with the development of guidelines for good care, quality improvement initiatives have been established in some countries, with Belgium playing a pioneering role with the IQED-Foot project. Within the DFU care context, providing optimal care, tracking practice variations and aligning performance is equally demanding.

Different approaches, frameworks and data sources have been provided in quality of care measurement. While querying existing data collections for developing QIs has been endorsed, collecting the existing scientific knowledge and establishing consensus among stakeholders seems to be just as important. QIs that serve as a basis for quality monitoring, must meet certain criteria to be useful. QIs must be developed with scientific rigor (valid and reliable), taking into account the availability of the necessary information for establishing the measure (feasible) and covering all aspects of care to provide a balanced and comprehensive picture of healthcare quality (multidimensional).

To establish the existing quality improvement initiatives and QIs in diabetic foot care, several pioneers in the diabetic foot field worked together to systematically review all the literature available at that time and based their work on the input of key opinion leaders in the field when literature was not available. Since then, however, interest in diabetic foot care has grown considerably, as have the number of publications. A systematic search of the literature on interventions that could be used as QIs was not carried out again. Further, no formal consensus has been conducted among diabetic foot stakeholders. In addition, the QIs used differ between national initiatives, are measured in slightly different (sub)populations, and do not monitor all aspects of care and of patient health and quality of life. Moreover, an appropriate strategy to compare QIs properly between DFCs still needs to be developed. To date, quality monitoring has continued to show significant variations in clinical practice between diabetic foot services, both between and within countries. These shortcomings need to be addressed to upgrade quality monitoring within specialized multidisciplinary diabetic foot services, and ultimately to make it easier for HCP and policymakers to achieve quality improvement.

2.2 Aims and objectives of the PhD dissertation

The overall goal of this PhD was to optimize quality monitoring of DFU care in specialized diabetic foot services so that it becomes easier for HCP and policymakers to achieve quality improvement. More specifically, this PhD aims to provide methods that enables to identify valid, multidimensional and useful QIs to monitor and improve quality of care in DFCs, to achieve fair comparison and to broaden the scope of DFU care monitoring, based on the assumption that such a mix-method approach will reinforce the existing QIs and bring new insights.

For this purpose, three specific objectives were integrated into this PhD dissertation (Figure 2.1):

1. First, we aimed to develop a standardized approach to identify evidence-based structure and process QIs (track 1)
    a. In a first step, a scoping review was performed to identify candidates in the literature.
    b. The second step involved a diabetic foot care stakeholder panel to identify the most appropriate indicators using a modified Delphi consensus method.

2. A second objective was to refine and broaden the scope of DFU care monitoring (track 2).
    a. In a first sub-track, data from the existing large database of the QA initiative “IQED-foot” and risk-adjustment methods were used to develop and validate multivariable models that can be used for risk stratification or benchmarking (*Bottom-up approach)*.
    b. A second sub-track focused on PROMs for evaluating the emotional and physical functioning of patients with DFU. A monocentric study was conducted to assess the measurement properties of two questionnaires that may provide reliable patient HRQoL information.

3. Finally, we aimed to formulate recommendations for future directions for performing quality improvement in DFCs.

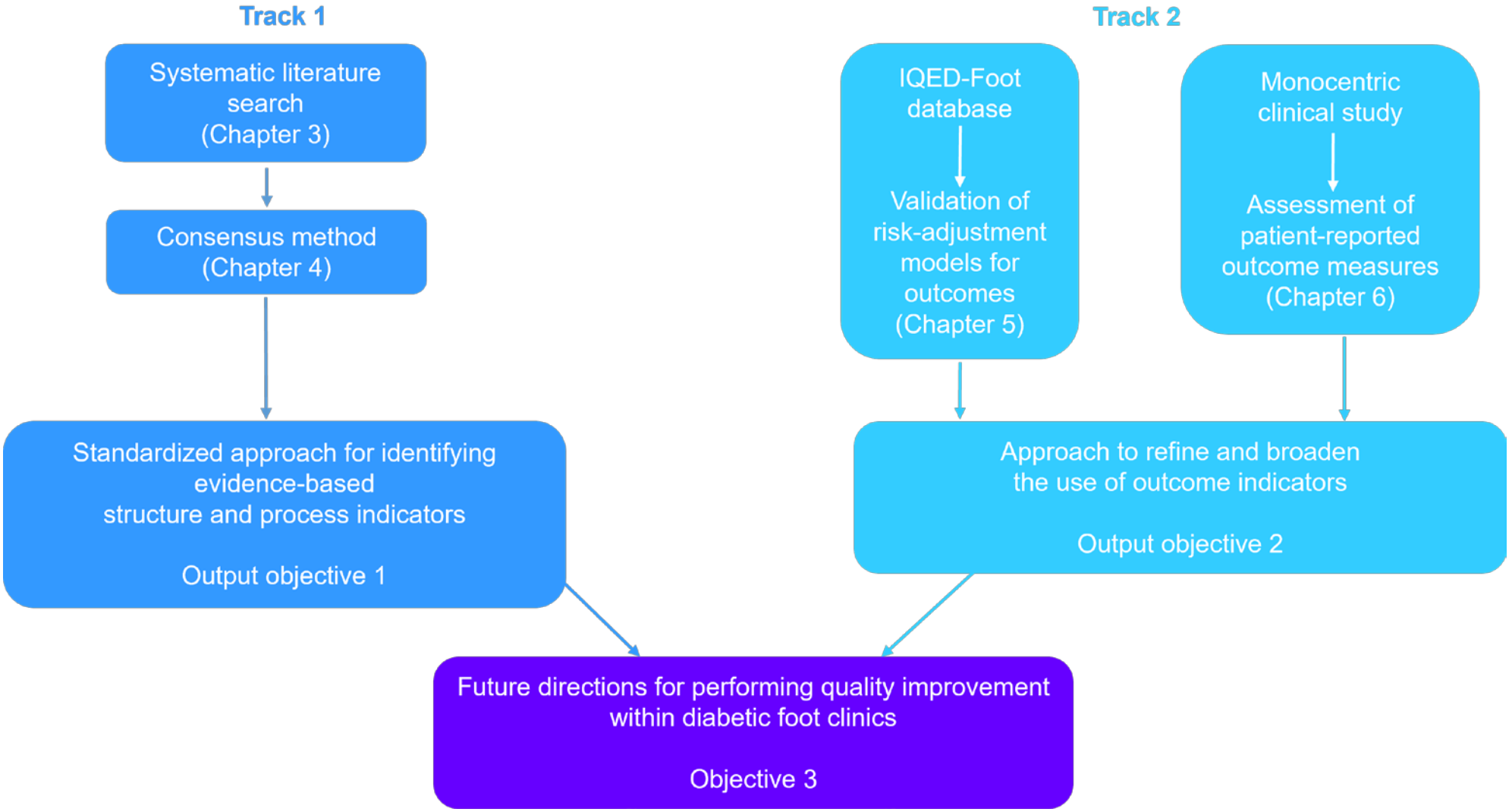

Figure 2.1 Overview of the different objectives, and chapters of this thesis

2.3 Outline of the dissertation

This dissertation is built up around the research objectives disseminated in the aforementioned section 2.2.

Chapter 3 and 4 described the identification of evidence-based structure and process QIs, using an open-minded approach, i.e. using clinical studies as primary sources (not limited to guidelines). The third chapter included the study result of the scoping review aiming to search for candidate QIs in the literature. The review provided an exhaustive overview of the available scientific evidence on interventions that could be used as evidence-based process or structure indicators. This overview was used to formulate a set of candidate QIs aimed to be evaluated by a diabetic foot care stakeholder panel. The fourth chapter described the formal consensus process used by the stakeholder panel to evaluate the candidates and to achieve consensus on the most relevant and feasible QIs to assess quality in DFCs.

Chapter 5 reported the bottom-up approach used to provide robust risk-adjustment models for comparing outcome QIs. The approach relied on the large nation-wide IQED-Foot database and addressed the common pitfalls encountered in risk-adjustment strategy. The rationale for conducting this study was to turn around the classical approaches that commonly selected determinants based on expert opinion (top-down approach). The information on determinants can be used to streamline treatment actions but also to study variations in outcomes that must be attributable to variations in care quality, which permits fair comparison between different diabetic foot services (benchmarking).

Chapter 6 attempted to identify potential sources of PROs. This chapter depicted the results of a monocentric study that aimed to assess the ability of HRQoL instruments to provide reliable PROs among Belgian-Dutch speaking patients with DFU. This study used consensus-based standards (COSMIN) and constituted the required first step for further validation. The rational for conducting this study was the limited use of patient-reported indicators for monitoring DFU care within DFCs.

Chapter 7 contained a general discussion of the methodology used in chapters 3 through 6 and the resulting topics covered by QIs from the perspective of DFU world and other fields. Those outputs were used to give advice for performing quality improvement in (Belgian) DFCs.

Chapter 3

EVIDENCE BASED INTERVENTIONS FOR IDENTIFYING CANDIDATE QUALITY INDICATORS TO ASSESS QUALITY OF CARE IN DIABETIC FOOT CLINICS: A SCOPING REVIEW

This chapter is based on:

Flora Mbela Lusendi, An-Sofie Vanherwegen, Kris Doggen, Frank Nobels, and Giovanni Arnoldo Matricali. “Evidence-Based Interventions for Identifying Candidate Quality Indicators to Assess Quality of Care in Diabetic Foot Clinics: A Scoping Review.” *BMC Public Health* 24, no. 1 (April 10, 2024): 996. https://doi.org/10.1186/s12889-024-18306-2.

3.1 Abstract

Background: Foot ulcers in people with diabetes are a serious complication requiring a complex management and have a high societal impact. Quality monitoring systems to optimize diabetic foot care exist, but a formal and more evidence-based approach to develop quality indicators (QIs) is lacking. We aimed to identify a set of candidate indicators for diabetic foot care by adopting an evidence-based methodology.

Methods: A systematic search was conducted across four academic databases: PubMed, Embase CINAHL and Cochrane Library. Studies that reported evidence-based interventions related to organization or delivery of diabetic foot care were searched. Data from the eligible studies were summarized and used to formulate process and structure indicators. The evidence for each candidate QI was described in a methodical and transparent manner. The review process was reported according to the PRISMA statements and its extension for Scoping Reviews.

Results: In total**,** 981 full-text articles were screened, and 322 clinical studies were used to formulate 42 candidate QIs.

Conclusions: An evidence-based approach could be used to select candidate indicators for DFU care, relating to the following domains: wound healing interventions, peripheral artery disease, offloading, secondary prevention, and interventions related to organization of care. In a further step, the feasibility of the identified set of indicators will be assessed by a multidisciplinary panel of diabetic foot care stakeholders.

Key words: Diabetic foot ulcer, Quality of healthcare, Quality indicators, Evidence-based medicine, Health service research

3.2 Introduction

DFU is a common disability burden, with a 25% lifetime risk in persons with diabetes;[139] it is estimated that 40 to 60 million people are globally affected by DFU.[23] The condition has an important impact on quality of life of both persons with diabetes and DFU and their informal caregivers [66,73] and causes substantial healthcare costs [23,74,153]. Because of the significant physical, psychosocial and economic impact of diabetic foot disease, there is a global search by the medical community for systems of quality evaluation and monitoring of diabetic foot care [146,148,154]. The “International Working Group on the Diabetic Foot” (IWGDF) recommends auditing all aspects of diabetic foot care to ensure that clinical practice meets accepted standards of care [155].

The management of DFU is complex and demanding. DFU care requires multidisciplinary collaboration across the healthcare landscape, in an often lengthy care process, in which not only the quality of the care provided by each individual healthcare provider is important, but also the quality of the collaboration and of the overall organization of the care.

Quality monitoring of such complex care is equally demanding. It requires several quality of care indicators (QIs) that describe the performance that should occur for a particular type of patient or the related health outcomes, followed by the assessment of whether patients’ care is consistent with the indicators based on evidence-based standards of care [117]. QIs can be related to structure, process or outcome of healthcare [102] and/or meet additional quality-of-care frameworks such as the six aims for the “21st Century Health Care System” provided by the IOM[105]. In order to be useful, they must be developed, tested and implemented with scientific rigor. For a care process to be considered as a valid QI, it must have been demonstrated to be associated with a desired outcome. Similarly, a structure of care can be used as QI, if it increases the likelihood of a desired outcome or of a process, which improves an outcome. Further, for outcome indicators to be valid, variations in outcomes must be attributable to variations in care quality [115]. Two key steps have been emphasized for developing QIs: the synthesis of information from a variety of sources (e.g. literature, clinical data) and a validated method to determine the extent to which experts agree about the proposed set of indicators [125].

In diabetic foot care, there already exist some national initiatives on quality evaluation and monitoring. Belgium, Germany and the UK have issued national quality initiatives for accreditation and auditing of diabetic foot services [63,150]. The German Working group on the Diabetic Foot developed a certification procedure for diabetic foot centres that includes data collection on structure of care and on limited parameters of process of care (e.g. vascular intervention) and outcome (e.g. rate of minor and major amputations) [148,156]. These indicators were defined by an expert board within the working group. In Belgium, indicators were developed by Belgian diabetic foot experts and used in the context of the nationwide quality initiative, named “IQED-Foot”. A large number of QIs are related to processes of care (e.g. revascularization of ischemic lower limbs) and to outcomes (e.g. ulcer healing rate) [143]. No indicators of structure of care are used, as only DFCs that meet the national requirements for accreditation participate in the quality evaluation.

In addition, the UK launched a “National Diabetes Foot Care Audit”, based on a pilot project that assessed methodology for the measurement of processes and outcomes in the management of DFUs using QIs defined by a national working group [146]. It included indicators related to diabetes management, ulcer outcome but also patient-reported outcome measures.

Although the data collections in the context of these audits are valuable, they have a number of shortcomings that need to be addressed. The QIs used differ from one initiative to another, and do not cover all aspects of care. The current indicators are largely based on expert opinion, without a systematic search of the literature nor any formal consensus among diabetic foot care stakeholders.

Therefore, there is a need for a more systematic and evidence-based approach to develop QIs for diabetic foot care. So far, a detailed methodology describing the identification of QIs in diabetic foot care has not been published. The purpose of this study was to perform a systematic and open-minded (i.e. not limited to guidelines) search of the literature on evidence-based interventions that could be used as process or structure indicators to assess quality in DFCs. The result of this work represented the first key step in developing a set of evidence-based QIs that will be used to achieve consensus among diabetic foot care stakeholders.

3.3 Methods

This scoping review was conducted to provide an overview of the available scientific evidence. The review process was reported according to PRISMA statements [157] and its extension for Scoping Reviews [158]. The results of the scoping review aim to be used to formulate a set of candidate QIs which are evaluated by a diabetic foot care stakeholder panel during a modified Delphi consensus.

Search strategy

We searched for systematic reviews and primary clinical studies to identify aspects of the organization of care (structure) or delivery of care (process) that could be defined as quality of care indicators. The topics “foot ulcer” or “amputation” combined with the topic “diabetes mellitus” were used to build the search strategy for four electronic databases: PubMed, Embase, CINAHL and Cochrane Library. Controlled terms from Medical Subject Headings (MeSH) in PubMed and Cochrane Library, from Emtree in Embase.com and from CINAHL Headings in CINAHL were used in the search query. A supplementary table shows the search query in detail (Supplementary table 3.6.1). We focused on producing a search strategy that was sensitive. To do so, we use more general terms, whilst avoiding specific search terms related to “quality of care” in order to not miss potentially eligible studies. In addition, a lot of research on the effectiveness of interventions do not phrase their results in terms of "quality of care", but simply in terms of improving outcomes.

The following publication types were excluded from the search strategy: letter, editorial, comment, case reports, and note. In addition, searches were limited to publications in English, French and Dutch. The search period ran from the inception of the databases to March 03, 2020.

Inclusion and exclusion criteria

To be eligible, a study had to fulfill all the criteria detailed in Table 3.1. Because of efficiency concerns, we applied a limitation on publication year. The review team (FML, ASV, KD, FN, GM) decided that the literature review would cover the period from 01/01/2011 to 03/03/2020 based on the assumption that the number of publications on diabetic foot has significantly increased over the last 10 years [159], and that therefore the relevant and up-to-date interventions will have been reviewed during the past 10 years. We searched for publications reporting clinical research studies that evaluated the effect of an intervention on health-related outcomes.

We included studies reporting interventions which addressed one of the following chapters covered by the guidelines provided by the IWGDF [160]: interventions to enhance healing of foot ulcers in persons with diabetes (wound healing interventions), peripheral artery disease (PAD), offloading and prevention of foot ulcers in patients with diabetes. Since the success in DFU management also depends on effective organizational features [155], we also covered interventions related to organization of care. We decided to not cover the domain of infection (e.g. antimicrobial therapy, adjunctive treatment and surgical treatment) since two extensive systematic reviews have been performed recently by the IWGDF, leading to updated Guidelines on the diagnosis and treatment of foot infection in persons with diabetes [161,162]. For the offloading domain, the treatment with “Total Contact Casting” (TCC) was proven to be efficient more than 10 years ago [163–167] and is nowadays commonly used as the gold standard. Therefore, TCC was not included in the evidence-based approach to develop QIs. Moreover, studies exclusively dealing with prevention of foot ulcers in people with diabetes without active or history of foot ulceration (primary prevention) were excluded because it did not inform us about the management of an existing DFU. We also excluded interventions reported by only one single study (not related to organization of care). The main criteria we used were: (i) studies designed with a control group (randomized or non-randomized) or systematic reviews of controlled studies; (ii) inclusion of patients with diabetes and an active or history of foot ulceration (including the different stages of the complication); (iii) description of an intervention related to the organization or delivery of diabetic foot care (diagnostic, treatment, secondary prevention): (iv) measuring change in outcomes related to the foot/limb or to the patient or to the healthcare costs.

Selection process

Following completion of the database searches, the extracted records were entered into the reference management software Zotero (*https://www.zotero.org/*). Three researchers (FML, KD, SC) independently merged search results and removed duplicates [168–171]. Then, one researcher (FML) uploaded the resulting records to the online application “Rayyan” [172] (*www.rayyan.ai*) to help in the assessment of studies. Two researchers (FML, KD) independently and blindly reviewed studies by titles and abstracts to assess their eligibility based on the criteria mentioned above. At several occasions, they met to discuss any disagreements regarding their selections until consensus was obtained.

The level of agreement between the two reviewers was assessed by calculating Cohen's kappa values [173]. The full-texts of records that appeared potentially eligible were retrieved by one reviewer (FML), who was helped by an administrative collaborator (VB). The same reviewer (FML) examined the obtained full-text records. If necessary, other members of the reviewer team (ASV, FN, GM) were consulted to make the final decision.

Table 3.1. Detailed description of the inclusion/exclusion criteria

Criteria	Inclusion criteria	Exclusion criteria
Language	French, Dutch and English	Any language other than French, Dutch or English
Publication year	From 01/01/2011 to 31/01/2021	31/12/2010 or earlier
Study type	A clinical research study that evaluates interventions on health-related outcomes, whose full-text could be retrieved from the KU Leuven Libraries collection with institutional access or whose full report was registered or indexed on the platform ClinicalTrials.gov	1) Case reports, conference abstracts, study protocols, letter, editorial, comments, note, review 2) A clinical trial registered on the platform ClinicalTrial.gov, whose the status has not been reported as "*completed"*
Study domain	Studies report interventions that address the following domain of diabetic foot care: • organization of care • wound healing • peripheral artery disease • offloading • prevention of foot ulcer in people with diabetes with active or history of foot ulceration (secondary prevention)	Studies report interventions that address the following domain of diabetic foot care: • diagnosis and treatment of foot infection (antimicrobial therapy, adjunctive treatment and surgical treatment) • prevention of foot ulcer in people with diabetes without active/history of foot ulceration (primary prevention)
Study design	1) Studies designed with a control group (randomized or non-randomized) 2) Systematic review of controlled studies, with or without meta-analysis	1) Studies addressing the wound healing or offloading domain which, based on the reported study design, do not provide high quality evidence (level of evidence[a] >2) 2) Studies which, based on the reported study design, do not provide quality evidence of at least level 3 - e.g. case-control, case series, etc. 3) Systematic reviews of a combination of studies with eligible and non-eligible designs 4) Systematic reviews which do not provide a synthetized conclusion (pooled results or general statements) about the effect of an intervention

Table 3.1. Continued

Criteria	Inclusion criteria	Exclusion criteria
Population	1) People with diabetes: • with active diabetic foot ulceration (DFU) or history of diabetic foot ulceration, it includes the different stages of the complication: critical limb ischemia (CLI) - infection/osteomyelitis - gangrene • having surgical wounds subsequent to a diabetic foot ulcer (post-operative wound) 2) Mixed or more comprehensive study population (e.g. chronic wounds, PAD patients) where results is reported for the eligible study population (active or history of ulceration)	1) People with diabetes (non-exhaustive list): with Charcot foot, venous ulcer, claudication, amputation not due to a DFU, acute limb ischemia 2) Mixed or more comprehensive study population (e.g. chronic wounds, PAD patients) where the eligible study population was not specifically studied

[a]Level of Evidence provided by Oxford Centre for Evidence-Based Medicine (OCEBM) http://www.cebm.net/wpcontent/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf

Data extraction

Firstly, we collected comprehensive information about each eligible study using a structured form. The following data were extracted: author, year of publication, study design, sample size, ulcer characteristics, the studies' exclusion criteria, period of follow-up, intervention type, description of intervention, number of patients randomized to each intervention arm, studied outcomes, and whether differences between study groups were statistically significant. The clinical studies were grouped according to the domains listed above. One reviewer (FML) extracted the data and another reviewer (ASV) checked the entered data. Next, we used a second structured form to group studies within each domain based on the intervention types and outcomes studied. For each study, we recorded if the intervention had a significant or a non-significant effect on the reported outcomes and we defined population parameters based on ulcer characteristics. We used this information to generate evidence-based statements.

An evidence-based statement frames the association between an identified intervention and an eligible outcome using the PICO (population, intervention, control and outcome) criteria. The association of intervention-outcome was established based on the set of eligible publications. Lastly, the generated evidence-based statements were used to phrase candidate quality of care indicators. Each candidate indicator was expressed as a proportion, with a given denominator, i.e. the population evaluated by the indicator, and a numerator, i.e. the portion of the denominator that satisfies the condition of the indicator.

Description of existing supporting evidence

We developed an easy-to-use scoring system to be able to describe the strength of evidence provided by a large amount of identified eligible studies. This allowed us to communicate the certainty of evidence supporting the association between an identified intervention and an outcome.

In this scoring system, we used three factors to determine the quality of a study: the study design, the sample size and the scientific impact of the journal in which the study was published.

1. For determining the quality of the study design we adapted the levels of evidence provided by the Oxford Centre for Evidence-Based Medicine (OCEBM) [174–176] (Table 3.2.).

Table 3.2. Levels of evidence for determining the quality of the study design

	Domains	
Levels of Evidence (LoE)	**Wound healing Offloading**	**Surgical procedures from wound healing domain, PAD, secondary prevention, organization of care**
Level 1	Systematic reviews of randomized controlled trials (RCTs), with or without meta-analysis	
Level 2	Randomized controlled trials Systematic reviews of a combination of RCTs and non-randomized controlled studies, or non-randomized controlled studies only, with or without meta-analysis	
Level 3	Not included	Non-randomized controlled studies: Controlled before-after studies, Interrupted Time-series, prospective cohort studies, retrospective cohort studies (propensity score matched, regression technique)

We targeted studies that provided high levels of evidence (level 1 or 2). However, because some designs are more difficult to set up for some domains of diabetic foot care, we also allowed level 3 evidence for studies reporting interventions related to organization of care, PAD, surgical procedures to enhance wound healing and secondary prevention, and/or outcomes related to healthcare costs.

2. Regarding the sample size, a cut-off was applied based on a median of participants for a parallel group trial reported by Chan *et al*. [177] and also adopted by the "CONSORT" guidelines [178]. A sample size of ≥ 32 participants per treatment group was considered as "High", while a sample size of < 32 participants per treatment group was considered as "Low".

3. The scientific impact was reported by using the Journal category ranking and quartiles based on the journal's impact factor and provided by the Journal Citation Reports (JCR) [179] (Supplementary table 3.6.2). The publication year of the article was used to select the quartile year.

Our scoring system attributed a weight or "evidence score" to each combination of the three criteria. A supplementary table shows the evidence score value attributed based on the three criteria (Supplementary table 3.6.3). The reduction in points was non-linear in order to reflect the impact of each factor on publication quality. Finally, an evidence score was assigned to each study, independent of the statistical significance/non-significance of the reported intervention effect.

Following this, a mean score was calculated for the collection of publications reporting the same intervention, subdivided according to outcome. A separate mean score was calculated for publications reporting a significant effect and publications reporting no significant effect. The certainty of the evidence-based statement was categorized based on the mean score of the collection of publications reporting a significant effect. However, the statement was downgraded by one category in cases where the mean evidence score of the publications reporting no significant effect was equal to or higher than the mean evidence score of the publications reporting a significant effect. A supplementary table shows the categories of certainty of the evidence-based statements (Supplementary table 3.6.4).

3.4 Results

Results of the search

The electronic search in online databases yielded a total of 46,826 records. The “PRISMA” flow diagram for the study selection process and reasons for exclusion is shown in Figure 3.1 After removal of duplicates and title/abstract screening, 1,598 records from 2011 up to March 2020 were selected for a full-text search. There were 617 records for which the full-text could not be retrieved either because the full-text was not retrievable from the KU Leuven Libraries collection with institutional access or because they were conference abstracts. We assessed 981 full-text articles for eligibility. A total of 322 clinical studies met our inclusion criteria and were used to develop candidate QIs. We excluded 659 of the assessed full-texts, most often because a detailed inspection showed that the publication did not report a clinical study that evaluates an intervention (non-eligible study type, n=177). Numerous studies were also ineligible because the results for outcomes of interest and/or a measure of statistical significance were not reported (non-eligible outcome, n=92).

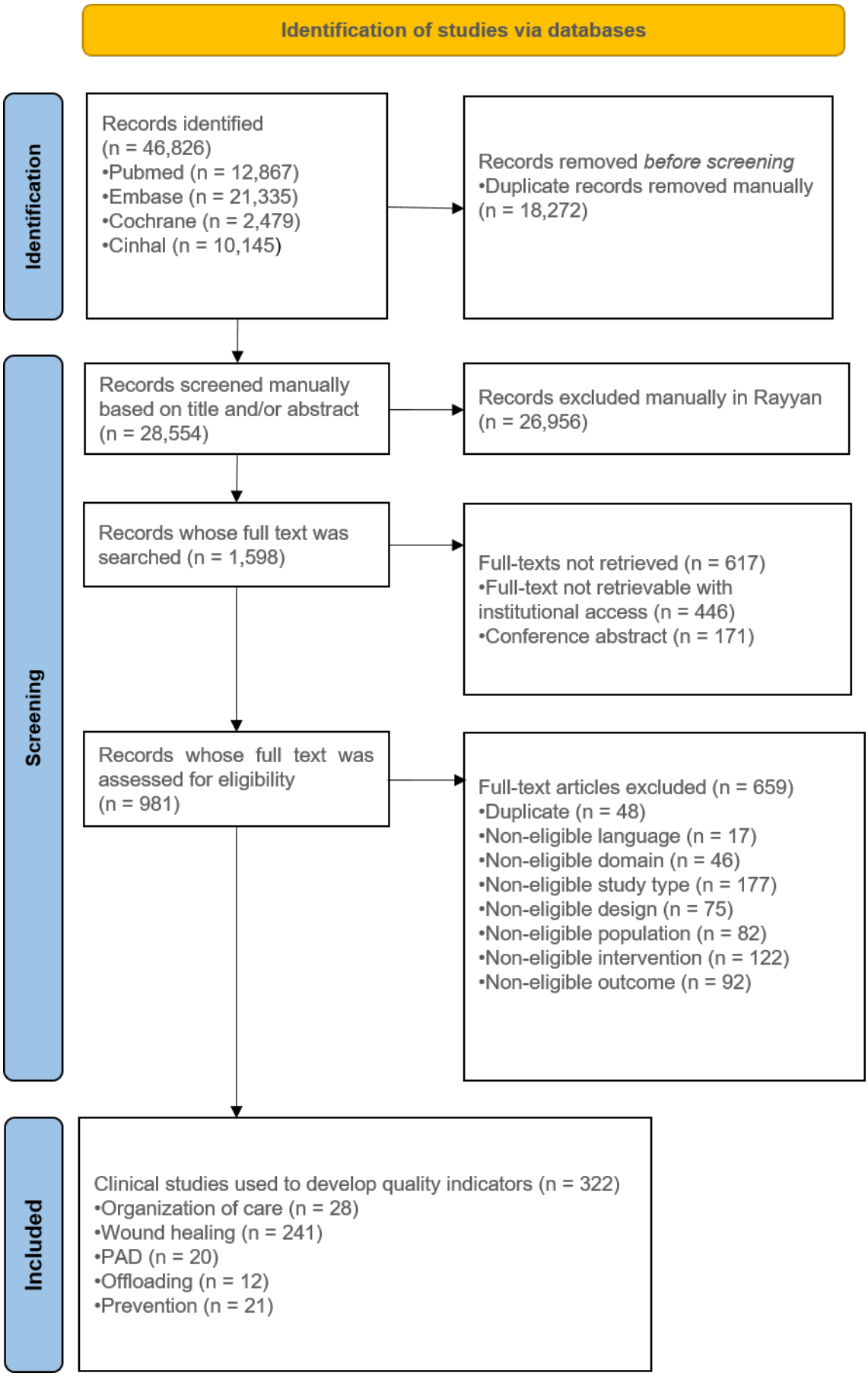

Figure 3.1. Study selection process and reasons for exclusion based on “PRISMA” flow diagram

A series of publications were excluded because of the reported type of intervention (non-eligible intervention, n=122); these were: interventions (not related to organization of care) supported by an only one single study, surgical procedures with another aim than revascularization, offloading, debridement or amputation, investigation of a single revascularization technique without control group, interventions based on natural agents only available in some areas (e.g. Chinese herbals, Papaya pulp dressing, Topical Kiwifruit), interventions outside of conventional clinical settings (e.g. home monitoring tools or telemedicine approach). Studies that regarded mixed or more comprehensive population (e.g. chronic wounds, PAD patients) that did not focus on our target population were also excluded (non-eligible study population, n=82). Others reasons for exclusion were the following: study designs which did not provide the expected level of evidence (non-eligible study design, n=75), the reported intervention was related to the infection domain (non-eligible domain, n=46), records were identified as duplicate after having checked the content of their full-text (duplicate, n=48), retrieved full-text was not in an eligible language although an English abstract was previously found (non-eligible language, n=17).

Included studies and evaluated interventions

The eligible clinical studies evaluated several types of interventions (see the references of included studies in Appendix 3.1). We defined subcategories for most intervention groups to represent our findings better. Among the 28 studies that addressed the *organization of care domain*, the following intervention groups were listed: introduction of multidisciplinary foot care, integration of a podiatric specialty in the multidisciplinary foot care team, implementation of a care management programme for diabetic foot, implementation of a Pay-for-Performance programme, implementation of nurse-led care. A large majority of studies (n=241) covered the *wound healing intervention domain* and evaluated the following interventions: non-biological dressings (2 subcategories: non-biological dressing impregnated with antimicrobial agents, non-biological dressing not impregnated with antimicrobial agents), bioengineered skin substitutes (3 subcategories: acellular dermal matrix, allogeneic skin substitute, autologous skin substitute), isolated cellular therapy, hyperbaric oxygen therapy (HBOT) (3 subcategories according to the patient perfusion status: not specified, adequate or inadequate), isolated growth factor, negative pressure wound therapy (NPWT), physical therapy (4 subcategories: laser/phototherapy, extracorporeal shockwave therapy, ultrasound therapy, physical therapy other than laser, shockwave or ultrasound), gas therapy (2 subcategories: topical oxygen therapy, ozone therapy or combined oxygen-ozone therapy), nutritional supplementation (2 subcategories: single nutrient supplementation, multi-nutrient supplementation), pharmacological agents (2 subcategories: action on vessels, action on immunity), debridement (2 subcategories: biological, enzymatic) and non-revascularization surgical procedures (3 subcategories: amputation, bony surgical offloading, soft tissue surgical offloading). The studies addressing the *PAD domain* (n=20) compared endovascular surgery and bypass surgery or evaluated the revascularization based on the angiosome concept. Among studies addressing the *offloading domain* (n=12), some evaluated offloading performed with non-removable knee-high offloading devices in comparison to offloading performed with removable knee-high offloading devices whilst others evaluated offloading performed with knee-high offloading devices in comparison to offloading performed with ankle-high devices.

The studies related to the *secondary prevention domain* included three types of interventions (n=21): patient education, footwear and/or insoles (2 subcategories: therapeutic footwear and/or custom-made insoles, or custom-made shoes with and without optimization by plantar pressure measurements) and the application of a prevention management programme.

Summary of evidence

In a nutshell, the potential beneficial effect of interventions related to *organization of care* on DFU outcomes was supported by low evidence. The evidence that indicates that interventions related to the *wound healing intervention domain* may have a beneficial effect on DFU outcomes was heterogeneous. Overall, a possible beneficial effect on ulcer healing by treatment with non-biological dressings not impregnated with antimicrobial agents, bioengineered skin substitutes, isolated cellular therapy, isolated growth factors and NPWT was supported by moderate to high evidence. Unlike treatment with laser/phototherapy, extracorporeal shockwave therapy, topical oxygen therapy or enzymatic debridement, the possible beneficial effect on ulcer healing by treatment with ozone therapy or combined oxygen-ozone therapy, single nutrient supplementation, pharmacological agents having action on immunity, or biological debridement was supported by low evidence.
In the *PAD domain*, low evidence indicates that revascularization with endovascular surgery compared to open vascular surgery may have a beneficial effect on limb salvage/amputation-free survival and amputation events. The same certainty of evidence was observed the other way around, when comparing revascularization with open vascular surgery to endovascular surgery. No studies were identified from the literature search with no revascularization as control group. Concerning the *offloading domain*, very high evidence indicates that non-removable knee-high offloading devices may have a beneficial impact on time to healing, when compared to removable knee-high offloading devices. In the *secondary prevention domain*, the effect of patient education was the most studied, but the evidence indicating a potential beneficial effect on diverse DFU outcomes was low. A complete overview of the evidence supporting the extracted interventions from the literature is available in supplementary table 3.6.5.

Candidate evidence-based indicators

A total of 42 candidate evidence-based QIs for studying quality of care in DFCs were developed from our findings from existing literature. An overview is presented in Table 3.3. They were attributed to the level of care (hospital, national) and the aspect of care addressed (structure, process or outcome).

Table 3.3. List of quality indicators per domain, developed from evidence-based interventions identified through a scoping review

Domain: Organization of care					
	Intervention	**Indicator**	**Numerator/Denominator**	**Level of care**	**Indicator type**
1	Introduction of multidisciplinary foot care	Proportion of people with a diabetic foot ulcer receiving multidisciplinary foot care	**Numerator**: The number of people with a diabetic foot ulcer receiving multidisciplinary foot care **Denominator**: The total number of people with a diabetic foot ulcer	Hospital National	Structure
2	Integration of a podiatric specialty in the multidisciplinary foot care team	Proportion of people with diabetic foot ulcer receiving multidisciplinary foot care with an integrated podiatric specialty	**Numerator**: The number of people with a diabetic foot ulcer receiving multidisciplinary foot care with an integrated podiatric specialty **Denominator**: The total number of people with a diabetic foot ulcer		
3	Implementation of a care management programme for diabetic foot	Proportion of people with a diabetic foot ulcer treated within the context of a care management programme for diabetic foot	**Numerator**: The number of people with a diabetic foot ulcer treated within the context of a care management programme for diabetic foot **Denominator**: The total number of people with a diabetic foot ulcer	National	
4	Implementation of a Pay-for-Performance programme	Proportion of diabetic foot clinics that participate to a pay-for-performance programme	**Numerator**: The number of diabetic foot clinics that participate to a pay-for-performance programme **Denominator**: The total number of diabetic foot clinics	National	
5	Implementation of nurse-led care	Proportion of people with a diabetic foot ulcer receiving nurse-led care	**Numerator**: The number of people with a diabetic foot ulcer receiving nurse-led care **Denominator**: The total number of people with a diabetic foot ulcer	Hospital National	

Table 3.3. Continued

Domain: Wound healing interventions					
	Intervention	**Indicator**	**Numerator/Denominator**	**Level of care**	**Indicator type**
6	Treatment with non-biological dressings	Proportion of people with a non-healing diabetic foot ulcer treated with non-biological dressing (umbrella indicator[a])	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with any kind of non-biological dressing **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process
7	Treatment with non-biological dressings	Proportion of people with a non-healing diabetic foot ulcer treated with non-biological dressing impregnated with antimicrobial agents	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with non-biological dressing impregnated with antimicrobial agents[b] **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process
8	Treatment with non-biological dressings	Proportion of people with a non-healing diabetic foot ulcer treated with non-biological dressing not impregnated with antimicrobial agents	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with non-biological dressing not impregnated with antimicrobial agents* **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process
9	Treatment with bioengineered skin substitute	Proportion of people with a non-healing diabetic foot ulcer treated with a bioengineered skin substitute (umbrella indicator[a])	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with at least one type of bioengineered skin substitute **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process
10	Treatment with bioengineered skin substitute	Proportion of people with a non-healing diabetic foot ulcer treated with acellular dermal matrix	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with acellular dermal matrix **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process
11	Treatment with bioengineered skin substitute	Proportion of people with a non-healing diabetic foot ulcer treated with allogeneic skin substitute	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with allogeneic skin substitute **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process

Table 3.3. Continued

Domain: Wound healing interventions					
	Intervention	**Indicator**	**Numerator/Denominator**	**Level of care**	**Indicator type**
12	Treatment with non-biological dressings	Proportion of people with a non-healing diabetic foot ulcer treated with autologous skin substitute	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with autologous skin substitute **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process
13	Treatment with isolated cellular therapy	Proportion of people with a non-healing diabetic foot ulcer treated with isolated cellular therapy	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with isolated cellular therapy **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process
14	Treatment with hyperbaric oxygen therapy	Proportion of people with diabetic foot ulcer treated with systemic hyperbaric oxygen therapy	**Numerator**: The number of people with a diabetic foot ulcer treated with systemic hyperbaric oxygen therapy **Denominator**: The total number of people with a diabetic foot ulcer	Hospital National	Process
15	Treatment with hyperbaric oxygen therapy	Proportion of people with a diabetic foot ulcer and adequate perfusion treated with systemic hyperbaric oxygen therapy	**Numerator**: The number of people with a diabetic foot ulcer and adequate perfusion treated with systemic hyperbaric oxygen therapy **Denominator**: The total number of people with a diabetic foot ulcer and adequate perfusion	Hospital National	Process
16	Treatment with hyperbaric oxygen therapy	Proportion of people with diabetic foot ulcer and inadequate perfusion treated with systemic hyperbaric oxygen therapy	**Numerator**: The number of people with a diabetic foot ulcer and an inadequate perfusion treated with systemic hyperbaric oxygen therapy **Denominator**: The total number of people with a diabetic foot ulcer and an inadequate perfusion	Hospital National	Process
17	Treatment with isolated growth factor	Proportion of people with a non-healing diabetic foot ulcer treated with isolated growth factor	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with isolated growth factor **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process
18	Treatment with negative pressure wound therapy	Proportion of people with a non-healing diabetic foot ulcer treated with negative pressure wound therapy	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with negative pressure wound therapy **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process

Table 3.3. Continued

Domain: Wound healing interventions					
	Intervention	**Indicator**	**Numerator/Denominator**	**Level of care**	**Indicator type**
19	Treatment with physical therapy	Proportion of people with a non-healing diabetic foot ulcer treated with laser/phototherapy	**Numerator**: Proportion of people with a non-healing diabetic foot ulcer treated with laser/phototherapy **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process
20	Treatment with physical therapy	Proportion of people with a non-healing diabetic foot ulcer treated with extracorporeal shockwave therapy	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with extracorporeal shockwave therapy **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process
21	Treatment with physical therapy	Proportion of people with a non-healing diabetic foot ulcer treated with ultrasound therapy	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with ultrasound **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process
22	Treatment with physical therapy	Proportion of people with a non-healing diabetic foot ulcer treated with physical therapy other than laser, shockwave or ultrasound	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with physical therapy other than laser, shockwave or ultrasound **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process
23	Treatment with gas therapy	Proportion of people with a non-healing diabetic foot ulcer treated with topical oxygen therapy	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with topical oxygen therapy **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process
24	Treatment with gas therapy	Proportion of people with a non-healing diabetic foot ulcer treated with ozone therapy or combined oxygen-ozone therapy	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with ozone therapy or combined oxygen-ozone therapy **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process

Table 3.3. Continued

Domain: Wound healing interventions					
	Intervention	**Indicator**	**Numerator/Denominator**	**Level of care**	**Indicator type**
25	Treatment with nutritional supplementation	Proportion of people with a non-healing diabetic foot ulcer treated with a single nutrient supplementation	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with a single nutrient supplementation **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process
26	Treatment with nutritional supplementation	Proportion of people with a non-healing diabetic foot ulcer treated with a multi-nutrient supplementation	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with multi-nutrient supplementation **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process
27	Treatment with pharmacological agents	Proportion of people with a non-healing diabetic foot ulcer treated with pharmacological agents having an action on vessels	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with pharmacological agents having an action on vessel **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process
28	Treatment with pharmacological agents	Proportion of people with a non-healing diabetic foot ulcer treated with pharmacological agents having an action on immunity	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with pharmacological agents having an action on immunity **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process
29	Treatment with debridement	Proportion of people with a non-healing diabetic foot ulcer treated with biological debridement	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with biological debridement **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process
30	Treatment with debridement	Proportion of people with a non-healing diabetic foot ulcer treated with enzymatic debridement	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with enzymatic debridement **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process

Table 3.3. Continued

	Intervention	Indicator	Numerator/Denominator	Level of care	Indicator type
Domain: Wound healing					
31	Treatment with surgical procedures	Proportion of people with a non-healing diabetic foot ulcer treated with amputation	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with amputation **Denominator**: The total number of people with a non-healing diabetic foot ulcer	Hospital National	Process
32		Proportion of people with a non-healing diabetic foot ulcer treated with bony surgical offloading	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with bony surgical offloading **Denominator**: The total number of people with a non-healing diabetic foot ulcer		
33		Proportion of people with a non-healing diabetic foot ulcer treated with soft tissue surgical offloading	**Numerator**: The number of people with a non-healing diabetic foot ulcer treated with soft tissue surgical offloading **Denominator**: The total number of people with a non-healing diabetic foot ulcer		
Domain: Peripheral Artery Disease (PAD)					
34	Revascularization	Proportion of people with diabetic foot ulcer and inadequate perfusion treated with endovascular surgery	**Numerator**: The number of people with a diabetic foot ulcer and inadequate perfusion treated with endovascular surgery **Denominator**: The total number of people with a diabetic foot ulcer and inadequate perfusion	Hospital National	Process
35		Proportion of people with diabetic foot ulcer and inadequate perfusion treated with open vascular surgery	**Numerator**: The number of people with a diabetic foot ulcer and inadequate perfusion treated with open vascular surgery **Denominator**: The total number of people with a diabetic foot ulcer and inadequate perfusion		
36		Proportion of people with diabetic foot ulcer and inadequate perfusion undergoing revascularization based on the angiosome concept	**Numerator**: The number of people with a diabetic foot ulcer and inadequate perfusion undergoing revascularization based on the angiosome concept **Denominator**: The total number of people with a diabetic foot ulcer and inadequate perfusion		

Table 3.3. Continued

	Intervention	Indicator	Numerator/Denominator	Level of care	Indicator type
Domain: Offloading					
37	Offloading with non-removable knee-high devices	Proportion of people with a non-infected, non-ischemic plantar neuropathic diabetic foot ulcer treated with a non-removable knee-high offloading device	**Numerator**: The number of people with a non-infected, non-ischemic plantar neuropathic diabetic foot ulcer treated with a non-removable knee-high offloading device **Denominator**: The total number of people with a non-infected, non-ischemic plantar neuropathic diabetic foot ulcer	Hospital National	Process
38	Offloading with knee-high offloading devices	Proportion of people with a non-infected, non-ischemic plantar neuropathic diabetic foot ulcer treated with a knee-high offloading device	**Numerator**: The number of people with a non-infected, non-ischemic plantar neuropathic diabetic foot ulcer treated with a knee-high offloading device **Denominator**: The total number of people with a non-infected, non-ischemic plantar neuropathic diabetic foot ulcer		
Domain: Prevention					
39	Patient education	Proportion of people with a (history of) diabetic foot ulcer receiving patient education	**Numerator**: The number of people with a (history of) diabetic foot ulcer receiving patient education **Denominator**: The total number of people with a (history of) diabetic foot ulcer	Hospital National	Process
40	Footwear and/or insoles	Proportion of people with a history of peripheral neuropathy (PNP) receiving therapeutic footwear and/or custom-made insoles, or custom-made shoes	**Numerator**: The number of people with a history of PNP receiving therapeutic footwear and/or custom-made insoles, or custom-made shoes **Denominator**: The total number of people with a history of PNP		
41		Proportion of people with a history of diabetic foot ulcer receiving optimization by plantar pressure measurements of their custom-made footwear and/or insoles	**Numerator**: The number of people with a history of diabetic foot ulcer receiving optimization by plantar pressure measurements of their custom-made footwear and/or insoles **Denominator**: The total number of people with a (history of) diabetic foot ulcer		
42	Protocol-driven multidisciplinary prevention	Proportion of people with a (history of) diabetic foot ulcer treated within the context of a prevention management programme for diabetic foot	**Numerator**: The number of people with a (history of) diabetic foot ulcer treated within the context of a prevention management programme for diabetic foot **Denominator**: The total number of people with a (history of) diabetic foot ulcer		

[a] umbrella indicator = unifying indicator under which the specific and related interventions was grouped and which allows to assess the delivery of such therapy regardless the type
[b] honey derivatives, silver or antibiotics

3.5 Discussion

There is a need for a more evidence-based approach in the development of QIs for diabetic foot care. In this study, we adopted a systematic approach to search for evidence-based interventions from the existing literature and to formulate, based on an evaluation of our search findings, evidence-based candidate QIs on the structures and processes of care. It is not our intention to displace existing, deeply rooted QIs, but to propose additional candidate indicators in an evidence-based manner that can reinforce existing indicators. This evidence-based approach does not take into account clinical relevance or feasibility. We therefore consider this a first step in which possible indicators are collected for which good evidence exists, and then in a next step a stakeholder panel will decide which indicators are useful and feasible for implementation in quality monitoring.

Our evidence-based selection approach resulted in the collection of 42 candidate QIs, including 5 structure indicators and 37 process indicators. Although we only based our methodology on clinical studies, not on guidelines, our resulting candidate QIs span the majority of domains defined by the IWGDF guidelines.[155] Among these are several well-known process indicators, already in use in ongoing quality promotion initiatives (Belgium, Germany, UK), but we also proposed several additional indicators. Our indicators included a larger range of interventions and covered several topics that are not used in many quality evaluation systems and for which clinical interest has been growing. Examples are, nutritional status,[180,181] use of lipid-lowering therapy,[182] and of new therapies like cellular therapies[183] or topical oxygen therapy.[184] Despite the fact that for some of these candidate indicators no randomized controlled trials are available (or feasible), these processes are already part of clinical practice and could receive attention as QIs during the evaluation by a stakeholder panel.

In the domain of organization of care we selected indicators commonly reported in the literature such as the establishment of a multidisciplinary team approach or the integration of podiatric care but also less frequent indicators such as the implementation of protocolized care or of pay-for-performance, not implemented by most DFCs so far.[63]

In our review, interventions on patient health-related quality of life (QoL) were not included, although the assessment of the patient well-being and function through patient-reported outcome instruments is already proposed as process of care indicator in the UK[146]. This might be explained by the fact this domain is still in full development. Literature that investigates the relationship between psychological interventions and DFU outcomes is still scarce[69], and thus too limited to be able to make evidence based recommendations on QIs.

We did not aim to generate outcome of care indicators in this study because they are already considered as an important goal in diabetic foot care.

Besides, the methodology to identify and validate such QIs differs from the approach used in this study. It requires adjustment for differences in case mix and other external factors to ensure fair comparisons among institutions or physicians [185,186].

The availability of good quality studies providing high level of evidence was limited for topics such as organization of care or surgical procedures. Recently, considering that it is unlikely that studies of the effectiveness of revascularisation versus best medical and wound therapy alone will be conducted in patients with DFUs, proposals have been formulated to produce higher quality studies in the PAD domain.[187,188]. Conversely, numerous studies with high evidence were found to support the indicators addressing wound healing interventions and more particularly new therapies like bioengineered skin substitutes or isolated cellular therapy. This can be attributed to the great expansion observed for this body of research over the last decade. Nevertheless, practical concerns could arise in using these wound care procedures as QIs in routine care. For instance, issues may rise regarding the storage of such products that requires specific conditions to maintain cell viability. Another challenge may be related to their varied effects and high cost, making it difficult for clinicians to determine which product is appropriate for the patient. This is a clear example of candidate QIs that need the next step of evaluation by a stakeholder panel to decide if they are feasible for implementation in quality monitoring.

Our detailed methodology contributes to the field by using clinical studies as primary sources for possible quality measurements rather than guidelines, predominantly used for the development of QIs so far [189]. A practical guideline presents a framework for optimal care in the context of complex medical decision-making. However, it may reflect the views of the stakeholders involved in its development and quality measures that can be derived from it may be limited in scope. Our open-minded systematic search in the literature helped to identify domains and indicators of quality of care that are not (yet) considered by expert panels. In addition, we have listed the scientific evidence for each candidate QI in a methodical, precise and transparent manner. We developed an easy-to-use scoring system, based on objective criteria, to be able to describe the strength of evidence provided by a large amount of identified eligible studies in an easy to understand format for a stakeholder panel that need to judge on the feasibility of the candidate indicators. The fact that we did not use the standard systems commonly used for assessing certainty of evidence could be seen as a limitation. Yet, this is mainly due to the purpose of our study. We did not need to apply detailed criteria such as heterogeneity or publication bias because our aim was not to judge about the estimate of an effect [190].
We conducted a literature review to provide an exhaustive overview of the existing evidence that demonstrates the linkage between an intervention and an outcome, and thus the possible use of that intervention as a structure or process indicator to assess quality in DFCs. In a next step, the described evidence will be used as a supportive element in order to guide a stakeholder panel in their selection of appropriate QIs. Furthermore, if we were to use standard systems, we would have to use several tools to fit to the heterogeneous encountered designs, which will have made our work more complicated, considering the number of studies that we included.

We have limited ourselves to articles from the last 10 years, to keep the number of articles under review feasible, but also to reflect the current practice in DFCs. However, we strongly realize that the evidence for several pre-existing QIs is based on older literature and do not question it. An example is the use of TCC as a gold standard for offloading. A further limitation of our study is that a single review author examined the full-texts of the selected articles, conducted data extraction and rated the evidence. Because these tasks were not conducted dually and independently, we may have introduced some risk of errors. Nonetheless, a large number of records were assessed during the abstract/title phase, which have been performed independently by two reviewers. The calculation of inter-rater reliability (Cohen's kappa value) indicated an adequate agreement between the two reviewers, which increased the reliability of the selected records used for the next selection steps. Full-texts were assessed using straightforward criteria and the reviewer team was frequently consulted to check the plausibility of the decision.

In conclusion, we showed that it is possible to select a set of candidate indicators for diabetic foot care in an evidence-based manner, independently of expert opinion. In this way, various indicators emerged that are not commonly used in quality evaluation of diabetic foot care. In a next step, the identified set of candidate indicators were assessed for relevance and practical usefulness by a broad stakeholder panel from all levels of diabetes foot care. A formal methodology was used to stimulate the discussion and measure the collective opinion in an objective way [191]. In a later stage, it will be recommended to perform an impact analysis to evaluate whether implementation of these QIs changes processes of care and improves patient outcomes and/or reduces costs [125]. Furthermore, the update of these QIs will be monitored based on the evolving DFU care needs.

3.6 Supplementary figures and tables

Supplementary table 3.6.1. Search strategy

	In Pubmed	In Embase	In Cochrane	In Cinahl
#1	“Foot Ulcer” [Mesh]	'foot ulcer'/exp	[mh "Foot Ulcer"]	MH "Foot Ulcer+"
#2	"Amputation” [MeSH Terms:NoExp]	'below knee amputation'/exp	[mh ^Amputation]	(MH "Below knee amputation") OR (MH "Above knee amputation"))
#3	foot-ulcer* [tiab]	‘foot ulcer*’:ti,ab,kw	(foot NEXT ulcer*): ti,ab,kw	TI ("foot ulcer*") OR AB ("foot ulcer*")
#4	plantar-ulcer* [tiab]	'plantar-ulcer'/exp OR 'plantar-ulcer*':ti,ab,kw	(plantar NEXT ulcer*): ti,ab,kw	TI ("plantar ulcer*") OR AB ("plantar ulcer*")
#5	amput* [tiab]	'amput*':ti,ab,kw	(amput*): ti,ab,kw	TI ("amput*") OR AB ("amput*")
#6	"diabetes mellitus" [MeSH Terms]	'diabetes mellitus'/exp	[mh " diabetes mellitus"]	(MH diabetes+)
#7	diabet* [tiab]	'diabet*': ti,ab,kw	(diabet*): ti,ab,kw	TI (diabet*) OR AB (diabet*)
#8	diabetic-foot [tiab]	diabetic foot'/exp OR ‘diabetic foot’:ti,ab,kw	("diabetic foot"):ti,ab,kw	TI ("diabetic foot") OR AB ("diabetic foot")
#9	diabetic-feet [tiab]	‘diabetic feet’:ti,ab,kw	("diabetic feet"):ti,ab,kw	TI ("diabetic feet") OR AB ("diabetic feet")

Supplementary table 3.6.1. Continued

	In Pubmed	In Embase	In Cochrane	In Cinahl
#10	Letter [Publication Type]	'Letter'/exp		PT (Letter)
#11	Editorial [Publication Type]	'Editorial'/exp		PT (Editorial)
#12	Comment [Publication Type]	'Note'/exp		PT (Commentary)
#13	Case-reports [Publication Type]			
#14	#1 OR #2 OR #3 OR #4 OR #5	#1 OR #2 OR #3 OR #4 OR #5	#1 OR #2 OR #3 OR #4 #5	#1 OR #2 OR #3 OR #4 #5
#15	#6 OR #7	#6 OR #7	#6 OR #7	#6 OR #7
#16	#8 OR #9	#8 OR #9	#8 OR #9	#8 OR #9
#17	#10 OR #11 OR #12 OR #13	#10 OR #11 OR #12		#10 OR #11 OR #12
#18	#14 AND #15	#14 AND #15	#14 AND #15	#14 AND #15
#19	#18 OR #16	#18 OR #16	#18 OR #16	#18 OR #16
#20	#19 NOT#17	#19 NOT#17		#19 NOT#17
#21	#20 Filters: Publications in Dutch, English, French	#20 AND ([dutch]/lim OR [english]/lim OR [french]/lim)		#20 Narrow by Language : dutch/flemish, english, french

Supplementary table 3.6.2. Scientific impact reported by using journal category ranking and quartiles for determining the quality of the study

Category ranking	Quartile
Q1	Top 25%
Q2	Between top 25% and 50%
Q3	Between 50% and 75%
Q4	Bottom 25%

Supplementary table 3.6.3. Scoring system attributing an evidence score to each eligible study based on the levels of evidence, sample size and scientific impact

Evidence score	Level of Evidence	Sample Size	Scientific Impact
10	I	High	Q1
9	I	Low	Q1
9	I	High	Q2
8	I	Low	Q2
8	I	High	Q3
7	I	Low	Q3
7	I	High	Q4
6	I	Low	Q4
8	II	High	Q1
7	II	Low	Q1
7	II	High	Q2
6	II	Low	Q2
6	II	High	Q3
5	II	Low	Q3
5	II	High	Q4
4	II	Low	Q4
5	III	High	Q1
4	III	Low	Q1
4	III	High	Q2
3	III	Low	Q2
3	III	High	Q3
2	III	Low	Q3
2	III	High	Q4
1	III	Low	Q4

Supplementary table 3.6.4. Categories of certainty of the evidence-based statements based on the mean of evidence scores

Mean evidence score	Evidence statement category
≥ 9	There is very high evidence in literature that intervention I may...
≥ 8 and < 9	There is high evidence in literature that intervention I may...
≥ 7 and < 8	There is good evidence in literature that intervention I may...
≥ 6 and < 7	There is moderate evidence in literature that intervention I may...
< 6	There is low evidence in literature that intervention I may...

Supplementary table 3.6.5. Overview of the evidence supporting the extracted interventions from the literature. The certainty of the evidence supporting the association between an intervention and an outcome is indicated. The studies reporting a significant beneficial effect on outcome are in black, while the studies reporting a detrimental or no significant effect are in grey - see the references of included studies in Appendix 3.1

Supporting studies	Mean evidence score	Certainty of evidence-based statements	References
ORGANIZATION OF CARE DOMAIN			
Introduction of multidisciplinary foot care			
Ulcer healing			
1 study (III)	4	Low	(A1)
1 study (III)	3		(A2)
Major amputation events			
2 studies (II) - 9 studies (III)	4	Low	(A1,3–12)
3 studies (III)	4		(A2,13,14)
Minor amputations			
4 studies (III)	4	Low	(A1,A9,A13,A15)
2 studies (III)	2,5		(A2,A10)
Length of hospital stay			
3 studies (III)	4	Low	(A9,A13,A15)
2 studies (III)	3,5		(A2,A14)
Integration of a podiatric specialty in the multidisciplinary foot care team			
Ulcer healing			
2 studies (III)	2,5	Low	(A16,A17)
Major amputation events			
5 studies (III)	4	Low	(A17–A21)
Minor amputations			
1 study (III)	5	Low	(A18)
Length of hospital stay			
1 study (III)	4	Low	(A22)
Implementation of a care management program			
Ulcer healing			
1 study (III)	4	Low	(A23)
1 study (III)	3		(A24)
Major amputation events			
3 studies (III)	4	Low	(A23–A25)
1 study (III)	2		(A26)
Minor amputations			
1 study (III)	**3**	Low	(A25)
Mortality			
3 studies (III)	3	Low	(A23–A25)
Cost per patients			
1 study (III)	3	Low	(A25)
Implementation of a Pay-for-Performance program			
Non-traumatic lower extremity amputation events			
1 study (III)	4	Low	(A27)
Implementation of nurse-led care			
Patient-reported Experience Measures (PREMs)			
1 study (II)	6	Moderate	(A28)

Additional table 3.6.4. Continued

WOUND HEALING INTERVENTION DOMAIN			
Treatment with non-biological dressings impregnated with antimicrobial agents			
Ulcer healing			
2 studies (I) - 4 studies (II)	6,5	Low	(A29–A34)
2 studies (I) - 5 studies (II)	6,5		(A32)(A35–A40)
Ulcer area reduction			
3 studies (II)	4	Low	(A33,A37,A41)
2 studies (II)	5,5		(A42,A43)
Time to healing			
2 studies (II)	6	Moderate	(A30,A39)
2 studies (II)	5,5		(A37,A43)
Stump healing			
1 study (II)	6	Moderate	(A44)
Treatment with non-biological dressings not impregnated with antimicrobial agents			
Ulcer healing			
9 studies (I) - 6 studies (II)	8	High	(A34,A45–A58)
3 studies (II)	6		(A59–A61)
Ulcer area reduction			
9 studies (II)	5	Low	(A47,A50,A62–A68)
Time to healing			
6 studies (II)	6,6	Moderate	(A45–A47,A50,A51,A69)
Cost-effectiveness			
1 study (I) - 1 study (III)	5	Low	(A49,A70)
1 study (III)	2		(A71)
Hospitalization days			
2 studies (III)	2,5	Low	(A72,A73)
1 study (III)	2		(A72)
Treatment with bioengineered skin substitutes: acellular dermal matrix			
Ulcer healing[a]			
2 studies (I) - 3 studies (II)	7,2	Moderate	(A74–A78)
1 studies (I) - 2 studies (II)	7,6		(A79–A81)
Ulcer healing at 6 weeks			
1 study (I)	9	Very high	(A82)
Ulcer healing at 12 weeks			
1 study (I) - 2 studies (II)	7	Good	(A82–A84)
Ulcer healing at 16 weeks			
1 study (I) - 2 studies (II)	7	Good	(A82,A85,A86)
Ulcer area reduction			
3 studies (II)	6	Moderate	(A78,A79,A87)
Time to healing			
1 study (I) - 1 study (II)	8	High	(A82,A83)
1 study (II)	7		(A81)
Ulcer recurrence			
1 study (II)	7	Moderate	(A81)
1 study (II)	7		(A86)
Amputation events			
1 study (I) - 1 study (II)	7,5	Good	(7A5,A80)
Quality of life			
1 study (II)	7	Good	(A86)

Additional table 3.6.4. Continued

Treatment with bioengineered skin substitutes: allogenic skin substitute			
Ulcer healing[a]			
4 studies (I) - 6 studies (II)	7	Moderate	(A74,A80,A88–A95)
1 studies (I) - 1 study (II)	7,5		(A95,A96)
Ulcer healing at 6 weeks			
1 study (I) - 4 studies (II)	7	Good	(A97–A101)
Ulcer healing at 12 weeks			
1 studies (I) - 8 studies (II)	7	Good	(A96–A100,A102–A105)
Ulcer healing at 16 weeks			
1 study (II)	7	Good	(A103)
Probability of ulcer healing			
1 study (I) - 5 studies (II)	6,8	Moderate	(A88,A93,A103,A104,A106,A107)
Ulcer recurrence			
1 study (II)	6	Low	(A108)
1 study (II)	7		(A93)
Ulcer area reduction at 16 weeks			
5 studies (II)	6,2	Moderate	(A91,A94,A100,A105,A109)
1 study (II)	6		(A110)
Amputation events			
1 study (I) - 1 study (II)	7,5	Good	(A80,A108)
1 study (II)[b]	4		(A91)
Time to healing			
2 studies (I) - 9 studies (II)	6,7	Moderate	(A88,A89,A92–A94,A97,A99,A100,A104,A106,A111)
1 study (II)	6		(A96)
Cost-effectiveness			
1 study (I) - 3 studies (II) - 2 studies (III)	5,8	Low	(A102,A104,A110,A112–A114)
Treatment with bioengineered skin substitutes: autologous skin substitute			
Ulcer healing[a]			
3 studies (II)	7,6	Good	(A115–A117)
1 study (II)	6		(A118)
Ulcer healing at 12 weeks			
1 study (II)	5	Low	(A96)
1 study (II)	6		(A118)
Probability of ulcer healing			
1 study (II)	8	High	(A115)
Ulcer area reduction			
2 studies (II)	7	Good	(A117,A118)
1 study (II)	5		(A96)
Time to healing			
3 studies (II)	6,6	Moderate	(A96,A116,A117)
1 study (II)	6		(A118)
Treatment with isolated cellular therapy			
Ulcer healing			
1 study (I) - 1 study (II)	7,5	Good	(A119,A120)
1 study (II)	7		(A121)
Ulcer area reduction			
1 study (II)	5	Low	(A122)
Time to healing			
1 study (I)	9	Very high	(A123)
1 study (II)	7		(A124)
Reduction of pain			
1 study (I)	9	Very high	(A119)
Reduction of amputation events			
1 study (I) - 1 study (II)	7,5	Good	(A119,A120)

Additional table 3.6.4. Continued

Treatment with systematic hyperbaric oxygen in people with DFU			
Ulcer healing[c]			
2 studies (I) - 6 studies (II)	7,25	Moderate	(A125–A131)
2 study (I) - 3 studies (II)	8		(A131–A135)
1 study (III) [d]	5		(A136)
Ulcer area reduction			
2 studies (I) - 2 studies (II)	6,75	Low	(A134,A135,A137,A138)
1 study (I) - 1 study (II)	7		(A128,A139)
Reduction of major amputation events[c]			
2 studies (I) - 4 studies (II)	8	Moderate	(A125,A129–A131,A133)
3 studies (I) - 2 studies (II)	8,2		(A131,A132,A134,A135,A139)
1 study (III) [d]	5		(A136)
Reduction of minor amputation events			
1 study (I) - 1 study (II)	7	Moderate	(A125,A131)
3 studies (I) - 2 studies (II)	8,4		(A130,A131,A134,A135,A139)
Quality of life			
3 studies (II)	5,6	Low	(A127,A138,A140)
1 study (II)	7		(A141)
Treatment with systematic hyperbaric oxygen in people with DFU and adequate perfusion			
Ulcer healing			
1 study (II)	5	Low	(A126)
1 study (III)[d]	5		(A136)
Treatment with systematic hyperbaric oxygen in people with DFU and inadequate perfusion			
Ulcer healing			
1 study (I) - 1 study (II)	8	Good	(A125,A130)
1 study (II)	8		(A133)
Ulcer area reduction			
1 study (II)	4	Low	(A137)
Reduction of major amputation events			
1 study (I) - 2 studies (II)	8	High	(A125,A130,A133)
Reduction of minor amputation events			
1 study (I) - 1 study (II)	8	High	(A125,A130)
Treatment with isolated growth factors			
Ulcer healing			
11 studies (I) – 6 studies (II)	8,6	High	(A143–A159)
2 studies (I)	8		(A160,A161)
Ulcer area reduction			
1 study (I) - 4 studies (II)	6,8	Low	(A143,A149,A150,A155,A162)
3 studies (I) - 3 studies (II)	6,8		(A153,A154,A160,A163–A165)
Time to healing			
3 studies (I) - 6 studies (II)	7	Moderate	(A144,A150,A151,A153,A154,A159, A166A–168)
1 study (I)	10		(A155)
Reduction of amputation events			
1 study (I) - 1 study (II)	7	Moderate	(A161,A165)
1 study (I) - 1 study (II)	7,5		(A155,A169)
Cost-effectiveness			
4 studies (III)	3	Low	(A170–A173)
1 study (III)	5		(A174)

Additional table 3.6.4. Continued

Treatment with negative pressure wound therapy			
Ulcer healing			
5 studies (I) - 2 studies (II)	7,8	Good	(A175–A181)
1 study (II)	7		(A182)
Ulcer area reduction			
4 studies (I) - 5 studies (II)	6,1	Moderate	(A175,A177–A180,A183–A186)
1 study (I)	6		(A187)
Time to healing			
3 studies (I) - 1 study (II)	7,7	Good	(A175,A177,A179,A180)
1 study (II)	4		(A186)
Reduction of amputation events			
2 studies (I) - 2 studies (II)	7,5	Good	(A176,A177,A185,A188)
1 study (I)	6		(A187)
Quality of life			
1 study (II)	4	Low	(A189)
Cost-effectiveness			
4 studies (III)	3,25	Low	(A190–A193)
Treatment with physical therapy: laser/phototherapy			
Ulcer healing			
3 studies (I)	9,6	Very high	(A194–A196)
2 studies (II)	5		(A197,A198)
Ulcer area reduction			
2 studies (I) - 12 studies (II)	5,9	Low	(A194,A195,A197, A199–A209)
1 study (II)	6		(A210)
Treatment with physical therapy: extracorporeal shockwave therapy			
Ulcer healing			
2 studies (I) - 2 studies (II)	7,25	Good	(A211–A214)
Ulcer area reduction			
1 study (I) - 2 studies (II)	6,6	Low	(A211,A213,A215)
2 studies (I) - 1 study (II)	7		(A211,A212,A216)
Time to healing			
1 study (II)	6	Moderate	(A217)
Treatment with physical therapy: ultrasound therapy			
Ulcer area reduction			
3 studies (II)	5,6	Low	(A218–A220)
2 studies (II)	4		(A221,A222)
Time to healing			
1 study (II)	5	Low	(A218)
Treatment with physical therapy: other than laser, shockwave or ultrasound			
Ulcer area reduction			
1 study (I) - 3 studies (II)	6,5	Moderate	(A223–A226)
1 study (II)	6		(A227)

Additional table 3.6.4. Continued

Treatment with gases therapy: topical oxygen therapy			
Ulcer healing			
3 studies (II)	6	Moderate	(A228–A230)
1 study (II)	5		(A231)
Ulcer area reduction			
3 studies (II)	6	Moderate	(A228,A230,A232)
Time to healing			
1 study (II)	5	Low	(A229)
Treatment with gases therapy: ozone therapy or combined oxygen-ozone therapy			
Ulcer healing			
1 study (II)	6	Low	(A233)
1 study (I) - 1 study (II)	7,5		(A234,A235)
Ulcer area reduction			
1 study (II)	6	Low	(A233)
1 study (I) - 1 study (II)	7,5		(A234,A235)
Time to healing			
1 study (II)	6	Moderate	(A236)
Amputation events			
1 study (II)	6	Moderate	(A236)
Treatment with nutritional supplementation: a single nutrient supplementation			
Ulcer healing			
5 studies (II)	5,8	Low	(A237–A241)
1 study (II)	7		(A242)
Treatment with nutritional supplementation: a multi-nutrient nutrient supplementation			
Ulcer area reduction			
1 study (I) - 1 study (II)	7	Good	(A243,A244)
Treatment with pharmacological agents having an action on vessels			
Ulcer area reduction			
2 studies (II)	5,5	Low	(A245,A246)
Quality of life			
1 study (II)	4	Low	(A247)
Treatment with pharmacological agents having an action on immunity			
Ulcer healing			
2 studies (II)	5	Low	(A248,A249)
1 study (II)	6		(A250)
Ulcer area reduction			
2 studies (II)	4,5	Low	(A249,A251)
1 study (II)	5		(A252)

Additional table 3.6.4. Continued

Treatment with debridement: biological debridement			
Ulcer healing			
1 study (II)	6	Low	(A253)
3 studies (II)	6,3		(A254–A256)
Ulcer area reduction			
1 study (II)	6	Moderate	(A257)
Time to healing			
2 studies (II)	5,5	Low	(A253,A256)
1 study (II)	6		(A255)
Reduction of amputation events			
2 studies (II)	6,5	Moderate	(A254,A256)
Cost-effectiveness			
2 studies (II)	6	Moderate	(A255,A257)
Treatment with debridement: enzymatic debridement			
Ulcer healing			
1 study (I)	10	Very high	(A254)
Cost-effectiveness			
1 study (III)	3	Low	(A258)
Treatment with surgical procedures: amputation			
Reduction of the risk of mortality			
1 study (III)	3	Low	(A259)
2 studies (III)	3,5		(A260,A261)
Beneficial impact on ambulatory function (QoL)			
1 study (III)	4	Low	(A262)
Treatment with surgical procedures: bony surgical offloading			
Reduction of the risk of mortality			
1 study (III)	2	Low	(A263)
Time to healing			
3 studies (III)	1,6	Low	(A263–A265)
1 study (III)	4		(A266)
Reduction of amputation events			
2 studies (III)	1,5	Low	(A265,A267)
Ulcer recurrence			
2 studies (III)	2	Low	(A263,A264)
1 study (III)	1		(A265)
Reduction hospitalization rate			
1 study (III)	2	Low	(A263)
Treatment with surgical procedures: soft tissue surgical offloading			
Ulcer recurrence			
1 study (I) - 1 study (III)	7	Moderate	(A268,A269)

Additional table 3.6.4. Continued

PERIPHERAL ARTERY DISEASE DOMAIN			
Revascularization with endovascular surgery (vs. open vascular surgery)			
Limb salvage/amputation-free survival			
2 studies (III)	2,5	Low	(A270,A271)
3 studies (III)	3		(A271–A273)
Amputation events			
1 study (III)	5	Low	(A274)
1 study (II) - 2 studies (III)	4,6		(A272,A275,A276)
Hospitalization days			
1 study (III)	3	Low	(A271)
1 study (III)	5		(A277)
Cost-effective			
1 study (III)	2	Low	(A278)
Revascularization with open vascular surgery (vs. endovascular surgery)			
Limb salvage/amputation-free survival			
3 studies (III)	4	Low	(A277,A279,A280)
3 studies (III)	3		(A271–A273)
Amputation events			
1 study (III)	5	Low	(A277)
1 study (II) - 1 study (III)	5,5		(A272,A275)
Ulcer healing			
1 study (III)	5	Low	(A280)
Revascularization based on the angiosome concept			
Limb salvage/amputation-free survival			
1 study (I) - 3 studies (III)	5,7	Low	(A281–A284)
4 studies (III)	3,7		(A282,A285–A287)
Post-operative wound healing			
1 study (I) -1 study (II) - 5 studies (III)	4,7	Low	(A281,A283–A285,A287–A289)
1 study (III)	5		(A282)
Time to healing			
1 study (III)	4	Low	(A281)

Additional table 3.6.4. Continued

OFFLOADING DOMAIN			
Offloading with non-removable knee-high offloading devices			
Ulcer healing			
3 studies (I) - 3 studies (II)	7,1	Moderate	(A290–A295)
3 studies (I) - 2 studies (II)	7,6		(A291,A295–A298)
Ulcer area reduction			
1 study (II)	4	Low	(A292)
1 study (II)	6		(A297)
Time to healing			
1 study (I)	10	Very high	(A296)
1 study (I) - 3 studies (II)	6,25		(A291,A293,A297,A298)
Offloading with a knee-high offloading devices			
Ulcer healing			
2 studies (I) - 1 study (II)	7,6	Good	(A290,A291,A295)
2 studies (I) - 3 studies (II)	6,8		(A290,A291,A293,A299,A300)
Time to healing			
2 studies (II)	6,5	Moderate	(A293,A295)
1 study (II)	6		(A300)
Ulcer area reduction			
1 study (II)	4	Low	(A301)
SECONDARY PREVENTION DOMAIN			
Patient education			
Ulcer incidence			
2 studies (I) - 1 study (II) - 2 studies (III)	5,8	Low	(A302–A306)
2 studies (I) - 1 study (II)	8		(A302,A303,A307)
Ulcer area reduction			
2 studies (III)	1	Low	(A308,A309)
Quality of life			
1 study (II) - 1 study (III)	4,5	Low	(A310,A311)
Pain			
1 study (II)	4	Low	(A312)
Length of stay			
1 study (II)	4	Low	(A312)
Providing therapeutic footwear and/or custom-made insoles, or custom-made shoes			
Plantar ulcer reduction and/or recurrence			
2 studies (I) - 1 study (II) - 1 study (III)	6,5	Low	(A290,A302,A313,A314)
2 studies (II)	6,5		(A315,A316)
Providing optimization by plantar pressure measurements of the custom-made footwear and/or insoles			
Ulcer incidence			
1 study (II)	8	High	(A317)
Ulcer incidence[e]			
2 studies (II)	7	Good	(A318,A319)
Treatment in the context of a prevention management program			
Treatment cost-effectiveness			
1 study (II) - 2 studies (III)	4	Low	(A320–A322)

[a]no specific follow-up time was reported
[b]results in favor of control group (not significant)
[c]This outcome is reported in a study (Elraiyah *et al*.) through two levels of evidence (level of evidence I and II)
[d]results in favor of control group (significant)
[e]but only if a sufficient compliance to wear the footwear is present

Chapter 4

A MULTIDISCIPLINARY DELPHI CONSENSUS TO DEFINE EVIDENCE-BASED QUALITY INDICATORS FOR DIABETIC FOOT ULCER CARE

This chapter is based on:
Flora Mbela Lusendi, An-Sofie Vanherwegen, Frank Nobels*, and Giovanni A. Matricali*. A Multidisciplinary Delphi Consensus to Define Evidence-Based Quality Indicators for Diabetic Foot Ulcer Care. European Journal of Public Health 34, no. 2
(April 3, 2024): 253–59.

4.1 Abstract

Background: Valid measures to assess quality of care delivered to patients with diabetes suffering from DFU care scarce. This study aimed to achieve consensus on relevant and feasible QIs among stakeholders involved in DFU care, and was conducted as the second part of a Belgian QI selection study that sought to identify QIs for DFU care.

Methods: A stakeholder panel, including caregivers from primary care and specialized disciplines active in diabetic foot care as well as a patient organization representative, was recruited. By using the RAND/UCLA Appropriateness Method, stakeholders were asked to rate a list of 42 candidate evidence-based indicators for appropriateness through a 9-point Likert scale. QIs were classified based on the median ratings and the disagreement index, calculated by the inter-percentile range adjusted for symmetry.

Results: At the end of a 3-phase process, 17 QIs were judged as appropriate. Among them, five were not previously described, covering the following topics: integration of wound care specialty in the multidisciplinary team, systematic evaluation of the nutritional status of the patient, administration of Low Density Lipoprotein (LDL)-cholesterol lowering medication and protocolized care (implementation of care and prevention management protocols).

Conclusions: The identified evidence-based QIs provide an assessment tool to evaluate and monitor quality of care delivered to DFU patients. Future research should focus on their complementarity with the existing QIs and their implementation in clinical practice.

Keywords: diabetic foot ulcer, quality of care, quality indicators, Delphi technique

4.2 Introduction

A quality of care indicator (QI) is defined as a measurable aspect of care (structure, process or outcome) for which there is sufficient evidence and/or consensus that it can be used to evaluate quality of care and its evolution.[102,118] Two main steps have been identified for the development of QIs: the collection of existing knowledge for the creation of potential QIs and the establishment of a consensus on the proposed QIs to be used.[115,192] The first step consists of synthetizing the scientific literature and/or supplemental sources (e.g. grey literature). However, for many areas of health care, the available evidence challenges the development of QIs. This may be due to limited or inconclusive scientific evidence or lack of evidence for the specific population of interest (with the need to extrapolate results from other patient populations).[192] These challenges can largely be addressed with the use of a consensus method as second step, which constitutes the most common formal approach to make decisions, generate ideas or establish a ranking when scientific evidence is inconclusive.[128] It is based on the involvement of a group of stakeholders, who discuss the topic taking into account different perspectives and providing a more nuanced input, considering clinical relevance and feasibility.

DFU is a multifactorial chronic condition with a global prevalence of 6,3% among people with diabetes[23] and with a huge impact on quality of life[66] and healthcare expenditure.[153] The condition is an advanced stage diabetes complication occurring in multimorbid patients with long diabetes duration, which is making treatment complex. To tackle this complexity, care is often organized in a multidisciplinary way, including endocrinologists, orthopaedic and vascular surgeons, podiatrists, diabetes nurses, wound care nurses and shoe technicians.[193,194] To optimize this complex care, systems of quality evaluation and monitoring have been implemented in some countries. For this purpose, QIs have been developed and implemented in the frame of national audit-feedback initiatives organized in collaboration with diabetic foot services.[63] For example, in Belgium, diabetic foot experts decided, based on their clinical experience, to focus on certain processes and outcomes of care as well as the patient-level parameters that might affect these. However, the QIs used up to now present some limitations. They have not been identified in an exhaustive manner and thus might not consider all aspects of care, nor all interventions that may provide opportunities to improve DFU outcomes. Furthermore, not all DFU stakeholders were represented during the indicator selection and a formal selection methodology was not applied.

The high societal impact and the complex management of DFU warrant efforts to address the identified limitations of existing QIs. The present study aims to describe a selection of evidence-based QIs for DFU care by a multidisciplinary stakeholder panel consisting of the previously mentioned care holders, using a formal consensus method. We do not aim to displace well-established QIs but rather to reinforce existing and identify new evidence-based QIs. The proposed list of candidate indicators was established based on a systematic and open-minded (not limited to guidelines) search of the literature and focused on structure and process QIs (Manuscript submitted for publication). This article describes the second key step in developing a set of evidence-based QIs for DFCs.

4.3 Methods

Literature review and identification of candidate Quality indicators

We conducted a scoping review in the literature to identify available evidence-based interventions that could be used as a process or structure indicator to assess quality in DFCs (Manuscript submitted for publication). In summary, we performed structured searches of four electronic databases (Pubmed, Embase, Cinahl and Cochrane Library) for publications between database inception and March 03, 2020. We selected studies reporting interventions related to organization or delivery of care based on defined eligible criteria. From the 322 clinical studies included, 37 process indicators and 5 structure indicators were generated. The set of 42 candidate indicators covered the following diabetic foot care domains: organization of care, wound healing interventions, peripheral artery disease (PAD), offloading and secondary prevention (Supplementary table 4.6.1).

Selection of stakeholder panel

Panel members were recruited to represent the disciplines corresponding to the staff involved in recognized Belgian DFCs,[63,151] including diabetologist, orthopaedic surgeon, vascular surgeon, podiatrist, diabetes nurse and/or wound care nurse and shoe technician. Besides these disciplines, the following stakeholder groups were considered: representative of the diabetes patient organization, general practitioner and employee of NIHDI, which is the national organization for social security and reimbursement.[195] Belgian multidisciplinary DFCs and the national general practitioner network were contacted. We aimed to include one Dutch-speaking and one French-speaking representative for each selected discipline to represent the main Belgian linguistic communities. English was used as common language since it constitutes the universal form of communication in science. To those who expressed their interest, a copy of curriculum vitae was requested. Candidates were selected based on their expertise and representativeness of their stakeholder group, on their availability at the meeting date and on their command of English. The panel consisted of four diabetologists, two vascular surgeons, three podiatrists (of which one also had a shoe technician background), two orthopaedic surgeons, one general practitioner, one diabetes nurse and one employee of NIHDI. The general practitioner was the chairperson of the Diabetes Association where both patients and professionals join forces and thus was committed to ensure that the patient voice is taken into account. Stakeholders were financially compensated with a gift voucher (retribution).

Selection of quality indicators based on the RAND/UCLA Appropriateness Methodology

The stakeholder panel followed the guidelines of the formal consensus process RAND/UCLA Appropriateness Method (RAM)[129] to select evidence-based QIs for DFCs. It consists of two rating phases, with a face-to-face meeting between the rating phases. The approach relies on evidence-based medicine to guide stakeholders, stimulates their discussions and facilitates the collective opinion. The process flowchart of the RAND/UCLA Appropriateness Method is outlined in Figure 4.1.

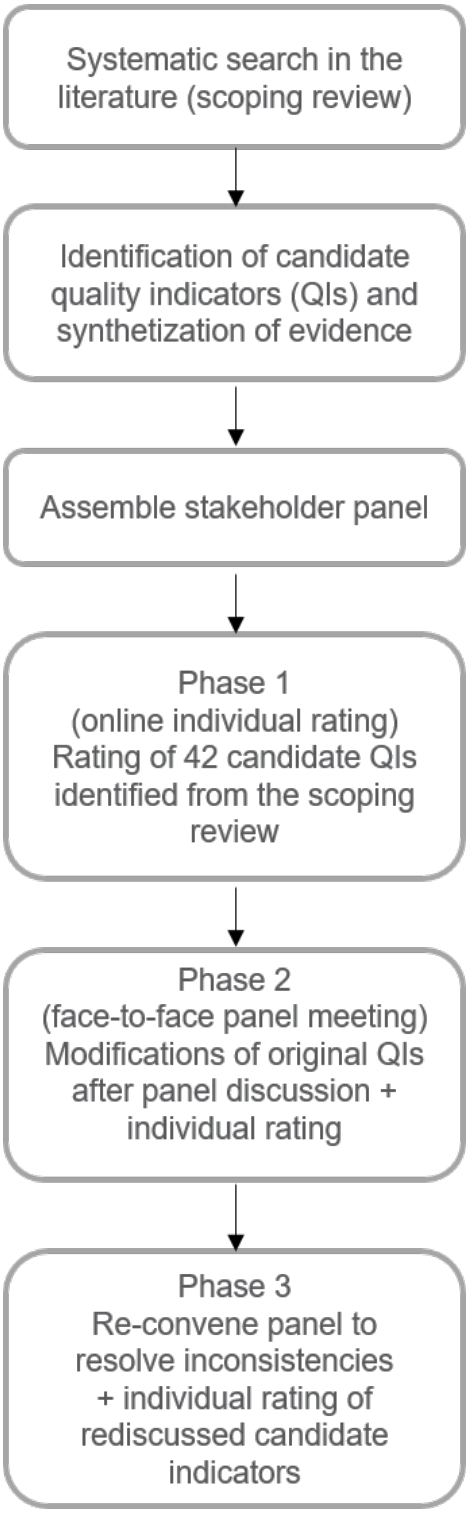

Figure 4.1. Process flowchart of the RAND/UCLA Appropriateness Method

In the first phase, panelists received an online survey along with the following documents: a summary document that provided information about the study background and the used methodology, a booklet describing each indicator, its characteristics and its synthetized supporting scientific evidence, the references of publications used to produce the candidate QIs and a glossary. The survey was administered through LimeSurvey. A personal access code (token) was provided to each panelist. Each panelist was asked to rate the 42 candidate indicators on their appropriateness by using the RAND/UCLA nine-point Likert-scale, defined as follows: 1=highly inappropriate, 5=intermediate rating; benefits and harms are about equal or the rater cannot make the judgement, 9=highly appropriate. Next, ratings of this first phase were analysed and summarized for the second phase. Based on the RAND/UCLA method, an indicator was classified into three levels of appropriateness, using the following definitions: appropriate (panel median of 7-9, without disagreement), uncertain (panel median of 4-6 or any median with disagreement), inappropriate (panel median of 1-3, without disagreement). The disagreement was quantified by using the RAND 'Disagreement Index' (DI).[129,196] The DI is defined as the ratio of two major elements: the inter-percentile range (IPR) (difference between 25th and 75th percentile) and the inter-percentile range adjusted for symmetry (IPRAS) (dispersion of scores). When DI is ≤1.0, no disagreement exists among the panelists. The lower the DI, the lower the level of disagreement (i.e. the higher the level of agreement). A Personalized Panelist Rating Sheet (Appendix 4.1) was prepared for the second phase in order to give the panelists the opportunity to discuss their ratings, in light of the information concerning the other panelists' ratings. For each indicator, the following items were indicated: the panelist's own ratings of phase 1 as well as the distribution of scores from the other panelists (individual panelist's ratings were kept confidential), the panel median score, its associated level of appropriateness and the level of disagreement.

The second phase consisted of a face-to-face meeting under the leadership of a moderator. A summary of phase 1 results was presented, focusing on the candidate indicators for which there was disagreement. The panelists were encouraged to share comments, to reflect on their own ratings from phase 1, and were given the opportunity to modify the formulation of the original indicators listed or to propose new indicators. During the meeting, each panelist rated the appropriateness of each indicator again, taking into account possible modifications that were proposed, regardless of whether a consensus was reached or not in phase 1.

After examining the ratings of phase 2, inconsistencies were observed. Based on the recommendations from the RAND/UCLA methodology for resolving inconsistencies,[129] the panel was convened at an additional meeting (phase 3) to discuss the issues. During this third meeting, which was organized remotely, panelists expressed their opinions on the observed issues. Afterwards, panelists were asked to rate the appropriateness of the re-discussed indicators by considering the exchanges that took place during the online discussion. For this purpose, an online survey was sent along with a report describing the meeting discussion. The scores assigned during phases 2 and 3 were used to determine a final set of QIs. Only the indicators with a median rating of ≥ 7 and with no disagreement based on DI were selected as QIs for DFCs.

4.4 Results

The evaluation of candidate QIs occurred in three distinct phases. In total, 13 panelists participated in the full 3-phase rating process. The shoe technician and the employee of NIHDI completed the first phase but were not able to participate to the next phases. Only the shoe technician could be replaced. An overview of the different rating steps of the QIs can be found in Figure 4.2.

Phase 1 - Rating of 42 candidate indicators

At the end of phase 1, from the 42 candidate indicators, 27 (64%) were classified as uncertain and 15 (36%) were classified as appropriate. The appropriate indicators included four indicators addressing the domain of organization of care (A.1 - A.2 - A.3 - A.5), four addressing the domain of wound healing (B.6 - B.11b - B.12b - B.12c), one addressing the domain of peripheral artery disease (C.1a), two addressing the domain of offloading (D.1 - D.2) and four addressing the domain of secondary prevention (E.1 - E.2a - E.2b - E.3).

Phase 2 - Face-to face meeting

During the face-to-face meeting in phase 2, the discussion focused on the 27 indicators, which were classified as uncertain after the first phase. Among this set of 27 indicators, the stakeholders suggested to group, introduce or re-define a certain number of candidate indicators. A first suggestion was to redefine the indicators addressing non-biological dressings (B.1a - B.1b - B.1c) and bioengineered skin substitutes (B.2a - B.2b - B.2c - B.2d) into two therapy-specific indicators, which would measure the integration of the wound care specialty within the multidisciplinary team (A.6 - A.7). A second suggestion was to group the three indicators addressing hyperbaric oxygen therapy (B.4a - B.4b - B.4c) into a single indicator without specifications on the target population (B.4). It was also suggested to combine the two indicators (B.9a - B.9b) addressing nutritional supplementation into a single indicator covering the evaluation of the nutritional status of the patient (B.9). Finally, a new indicator addressing mechanical debridement (B.11c) was introduced and the three indicators (C.1a - C.1b - C.1c) addressing the domain of peripheral artery disease were combined into a single indicator (C.1). These changes were made during the meeting and resulted in a reduced list of 18 indicators. Between the discussions, stakeholders were invited to rate each of the 18 indicators and were given the opportunity to modify their ratings of phase 1 in light of these exchanges. As a results, a list of 33 indicators (i.e. the list of 18 indicators under discussion and the 15 indicators already rated as appropriate during phase 1) were assessed during phase 2. Of the 33 candidate indicators, 16 indicators were classified as appropriate, 8 indicators as inappropriate and 9 as uncertain, which meant that a consensus could not be reached.

Phase 3 - Resolving inconsistencies

Among the nine indicators classified as uncertain, there were three indicators (A.7 - D.1 - D.2) for which misunderstandings among the stakeholders and inconsistencies in appropriateness classification were suspected. For the first one (A.7), the analysis of the phase 2 results showed that the necessary modifications to the formulation of the indicator were not applied in the same way by all stakeholders. It was not clear if two distinct indicators, specific to the therapy used, had to be introduced. For the other two (D.1 - D.2), we observed that a small shift in ratings had changed the appropriateness classification from appropriate in phase 1 to uncertain in phase 2.

As recommended in the RAND/UCLA approach, an additional meeting (phase 3) was organized to discuss these inconsistencies. Considering the fact that the objective of the RAND/UCLA method is not to force the panel to a consensus, the six other indicators for which a consensus could not be reached after phase 2, were not discussed during phase 3. The assessment of the three ‘inconsistent’ indicators discussed and rated at phase 3 were as follow: the stakeholders could not reach a collective opinion for the indicator addressing the treatment with a knee-high offloading device (D.2), whereas the indicator addressing the treatment with a non-removable knee-high offloading device was classified as appropriate (D.1). In addition, the definition of the indicator covering the integration of a wound care specialty within the multidisciplinary team (A.6) proposed during phase 2, was clarified to combine knowledge on non-biological dressings and bioengineered skin substitutes. The appropriateness of that indicator (A.6) was confirmed, which resulted to the elimination of the therapy-specific indicator (A.7).

Final selection of quality indicators

Considering the scores assigned during the phase 2 and 3, the group of stakeholders classified 17 QIs as appropriate without disagreement (see Table 4.1), 8 indicators as inappropriate without disagreement (Supplementary table 4.6.2) and 7 indicators classified as uncertain, meaning that a collective opinion could not be reached (Supplementary table 4.6.3).

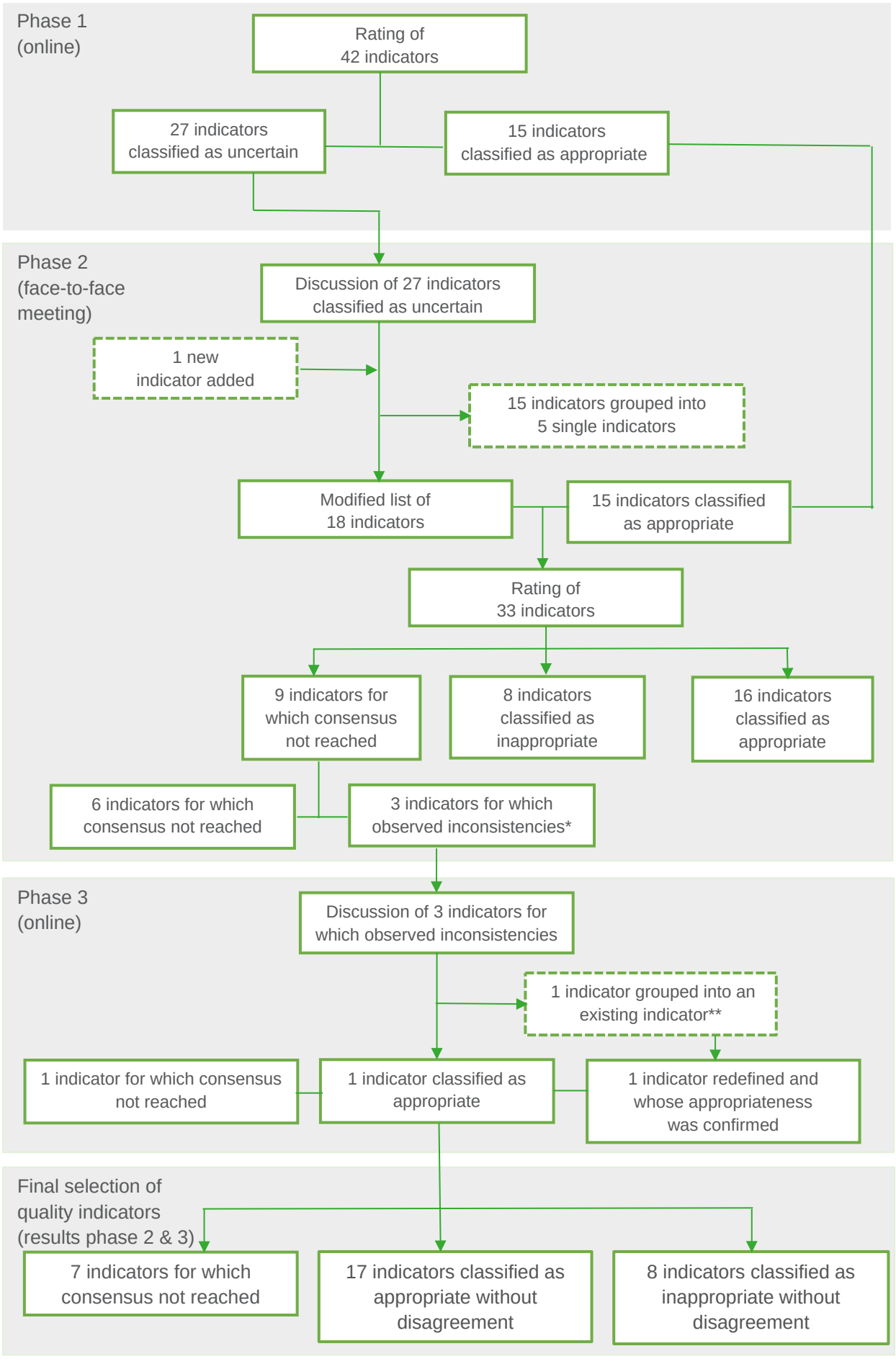
Phase 1
(online)
Rating of
42 indicators
27 indicators
classified as uncertain
15 indicators
classified as appropriate
Phase 2
(face-to-face
meeting)
Discussion of 27 indicators
classified as uncertain
1 new
indicator added
15 indicators grouped into
5 single indicators
Modified list of
18 indicators
15 indicators classified
as appropriate
Rating of
33 indicators
9 indicators for
which consensus
not reached
8 indicators
classified as
inappropriate
16 indicators
classified as
appropriate
6 indicators for which
consensus not reached
3 indicators for which
observed inconsistencies*
Phase 3
(online)
Discussion of 3 indicators for
which observed inconsistencies
1 indicator grouped into an
existing indicator**
1 indicator for which consensus
not reached
1 indicator classified as
appropriate
1 indicator redefined and
whose appropriateness
was confirmed
Final selection of
quality indicators
(results phase 2 & 3)
7 indicators for which
consensus not reached
17 indicators classified as
appropriate without
disagreement
8 indicators classified as
inappropriate without
disagreement

Figure 4.2. The 3-steps rating of the quality indicators
*****misunderstandings and unexplained shifts in the appropriateness classification
****** the formulation of indicator A.6 was modified to integrate indicator A.7 (*Proportion of people with a diabetic foot ulcer receiving multidisciplinary foot care with an integrated skin graft specialty*)

Table 4.1. List of appropriate indicators

No.	Indicator	Indicator type
Domain: Organization of care (4 indicators)		
A.1	Proportion of people with a diabetic foot ulcer receiving multidisciplinary foot care	Structure
A.2	Proportion of people with diabetic foot ulcer receiving multidisciplinary foot care with an integrated podiatric specialty	Structure
A.3	Proportion of people with a diabetic foot ulcer treated within the context of a care management programme for diabetic foot	Structure
A.6	Proportion of people with a diabetic foot ulcer receiving multidisciplinary foot care with an integrated wound care specialty	Structure
Domain: Wound healing (7 indicators)		
B.6	Proportion of people with a non-healing diabetic foot ulcer treated with negative pressure wound therapy	Process
B.9	Proportion of people with diabetic foot ulcer for whom the nutritional status has been evaluated	Process
B.10a	Proportion of people with a non-healing diabetic foot ulcer treated with LDL-cholesterol lowering medication	Process
B.11c	Proportion of people with a non-healing diabetic foot ulcer treated with mechanical debridement	Process
B.12a	Proportion of people with a non-healing diabetic foot ulcer treated with major amputation	Process
B.12b	Proportion of people with a non-healing diabetic foot ulcer treated with bony surgical offloading	Process
B.12c	Proportion of people with a non-healing diabetic foot ulcer treated with soft tissue surgical offloading	Process
Domain: Peripheral artery disease (PAD) (1 indicator)		
C.1	Proportion of people with a diabetic foot ulcer and inadequate perfusion treated with vascular surgery	Process
Domain: Offloading (1 indicator)		
D.1	Proportion of people with a non-infected, non-ischemic plantar neuropathic diabetic foot ulcer treated with a non-removable knee-high offloading device	Process
Domain: Secondary prevention (4 indicators)		
E.1	Proportion of people with a (history of) diabetic foot ulcer receiving patient education	Process
E.2a	Proportion of people with a history of peripheral neuropathy (PNP) receiving therapeutic footwear and/or custom-made insoles, or custom-made shoes	Process
E.2b	Proportion of people with a history of diabetic foot ulcer receiving optimization by plantar pressure measurements of their custom-made footwear and/or insoles	Process
E.3	Proportion of people with a (history of) diabetic foot ulcer treated within the context of a prevention management programme for diabetic foot	Process

4.5 Discussion

The aim of this study was to select evidence-based QIs for DFCs from a set of 42 candidate indicators identified from a systematic search in the literature (Manuscript submitted for publication). A multidisciplinary stakeholder panel was asked to score the appropriateness of QIs based on their clinical judgement and guided by the collected supporting evidence, using the formal RAND/UCLA Appropriateness approach.

Of the 17 QIs rated as appropriate by the stakeholder panel in this study, five QIs were addressing interventions that were not covered by the currently available QIs for diabetic foot care used in the different national initiatives on quality evaluation and monitoring.[143,150,156] A first QI not considered so far was an indicator measuring the integration of a wound care specialty in the multidisciplinary team. This indicator resulted from the combination of two sets of candidate indicators that measured the treatment with non-biological dressings and the treatment with bioengineered skin substitutes. Interestingly, the stakeholders validated the use of such therapies, on the condition that it was delivered by a health care provider who would master their use, which constituted a shift from a process indicator to a structure indicator. This can be seen as a trade-off between the stakeholder acknowledgement of the potential of such emergent therapies to enhance wound healing versus the complexity of their use, and thus the requirement of adequate skills. A second QI not considered so far was an indicator that addresses the evaluation of the nutritional status of the patient. This indicator allowed to introduce the rising topic of the impact of malnutrition on DFU outcomes.[181] Another QI not considered yet was an indicator which addresses the administration of Low Density Lipoprotein (LDL)-cholesterol lowering medication, which indicates the effect of the lipid profile on the DFU patient[182] and highlights the need for a more holistic view on treatment. Two additional “new” QIs addressed the implementation of care and prevention management protocols. This result underlines the fact that stakeholders believed that care structured by defined clinical management protocols indicates good quality of care.

At the end of the selection process, an agreement could not be reached for seven indicators (A.5 - B.4 - B7a - B10b - B11a - B.11b - D.2). This concerned indicators for which the stakeholder panel seemed to have divergent opinions because of equipment accessibility, heterogeneity of interventions reported in the literature or issues to determine a specific population. However, since one of the objectives of the RAND/UCLA method is to bring out the points of discordance or indecision, these indicators were not rated again during phase 3, except the indicator addressing the application of knee-high offloading devices (D.2). Among the seven indicators, three had been rated as appropriate during phase 1. However, the opinions expressed or the modifications performed during the panel meeting in phase 2 influenced their final rating. For instance, the rating as uncertain of the indicator addressing the treatment with enzymatic debridement (B.11b) might be attributed to the introduction of a new indicator addressing the treatment with mechanical debridement (B.11c) in phase 2. Another notable case, for which a consensus could not be reached while it had been rated as appropriate during phase 1, was the indicator addressing the application of knee-high offloading devices (D.2).

Together with the indicator addressing the application of non-removable knee-high offloading devices (D.1), this indicator was discussed again during phase 3 due to observed inconsistencies during analysis of phase 2. Finally, the indicator addressing the application of knee-high offloading devices (D.2) was rated as uncertain whereas the indicator addressing the application of non-removable knee-high offloading devices was rated as appropriate. In fact, these indicators were subjected to debate among the stakeholder panel, who highlighted the local realities (related to expertise or equipment availability) that make it difficult to apply such devices.

In our study, the selection of evidence-based QIs was conducted by using a formal and transparent methodology. Our approach, based on the RAND/UCLA Appropriateness method, relied on available scientific evidence, offered stakeholders a framework to discuss candidate QIs and included a quantitative method to measure their collective judgement. We recruited a panel representing the different disciplines active in diabetic foot care as well as a representative of the patient organization, which reflected the different expertise involved in the management of DFU. However, we could not recruit one Dutch-speaking and one French-speaking representative for each selected discipline. In addition, only Belgian stakeholders were included in the panel, which may limit the use of our results at an international level.

We complied with the main principle of the appropriateness method that consists of two separate, independent ratings in combination with a face-to-face stakeholder panel. An additional meeting had to be organized to resolve inconsistencies in the ratings observed in phase 2. Nevertheless, this did not impact the reliability and validity of our approach since recommendations to tackle such methodological issues have been provided by the developers of the method.[129] In the healthcare domain, the RAND/UCLA Appropriateness method has been widely used within quality-of-care research to identify valid quality measures.[197–200]

The selection of evidence-based QIs was limited by the fact that supporting high quality evidence was not available for some QIs. However, this is what stakeholder panels/consensus methods are dedicated for. When the highest level of evidence is not available, they aim to identify the processes of care that are most likely to be valid measures of quality.

Predictably, most of the QIs rated as appropriate addressed interventions which are commonly endorsed by the international guidelines of diabetic foot care.[83–86] This was logical since guidelines are also based on evidence and our panel of health care providers know the guidelines and put them into practice. Nevertheless, our use of an open-minded literature review to identify QIs rather than guidelines offers additional input. The use of literature, instead of guidelines brings new topics for QIs, but also allowed reflection on the feasibility of an indicator, regardless if the intervention has been recommended or not. The stakeholder panel did not feel obliged to accept the measure of an intervention because that intervention was endorsed by guidelines. They could put their judgement in perspective of their daily practice and the provided objective evidence.

In conclusion, we report the selection of a set of 17 evidence-based QIs for diabetic foot care by a multidisciplinary group of stakeholders from DFU care. We used a reliable methodology to fill the gaps identified in the development of existing QIs. Several indicators were introduced that were not previously described. The identified evidence-based QIs offer an open-minded view of the measures that can be used in DFCs to monitor and evaluate quality of care. In this study, we did not intend to question well-accepted QIs but rather to reinforce them and offer new evidence-based structure and process indicators. Further work is needed to evaluate the complementarity of these QIs with the existing QIs and their implementation in clinical practice.

4.6 Supplementary figures and tables

Supplementary table 4.6.1. List of 42 candidate quality indicators for studying quality in diabetic foot clinics per domain

No.	Indicator	Indicator type
Domain: Organization of care		
A.1	Proportion of people with a diabetic foot ulcer receiving multidisciplinary foot care	Structure
A.2	Proportion of people with a diabetic foot ulcer receiving multidisciplinary foot care with an integrated podiatric specialty	Structure
A.3	Proportion of people with a diabetic foot ulcer treated within the context of a care management programme for diabetic foot	Structure
A.4	Proportion of diabetic foot clinics that participate to a pay-for-performance programme	Structure
A.5	Proportion of people with a diabetic foot ulcer receiving nurse-led care	Structure
Domain: Wound healing interventions		
B.1a	Proportion of people with a non-healing diabetic foot ulcer treated with non-biological dressings (umbrella indicator[a])	Process
B.1b	Proportion of people with a non-healing diabetic foot ulcer treated with non-biological dressings impregnated with antimicrobial agents[b]	Process
B.1c	Proportion of people with a non-healing diabetic foot ulcer treated with non-biological dressings not impregnated with antimicrobial agents[b]	Process
B.2a	Proportion of people with a non-healing diabetic foot ulcer treated with a bioengineered skin substitutes (umbrella indicator[a])	Process
B.2b	Proportion of people with a non-healing diabetic foot ulcer treated with acellular dermal matrix	Process
B.2c	Proportion of people with a non-healing diabetic foot ulcer treated with allogeneic skin substitute	Process
B.2d	Proportion of people with a non-healing diabetic foot ulcer treated with autologous skin substitute	Process
B.3	Proportion of people with a non-healing diabetic foot ulcer treated with isolated cellular therapy	Process
B.4a	Proportion of people with a diabetic foot ulcer treated with systemic hyperbaric oxygen therapy	Process
B.4b	Proportion of people with a diabetic foot ulcer and adequate perfusion treated with systemic hyperbaric oxygen therapy	Process
B.4c	Proportion of people with a diabetic foot ulcer and inadequate perfusion treated with systemic hyperbaric oxygen therapy	Process
B.5	Proportion of people with a non-healing diabetic foot ulcer treated with isolated growth factor	Process
B.6	Proportion of people with a non-healing diabetic foot ulcer treated with negative pressure wound therapy	Process
B.7a	Proportion of people with a non-healing diabetic foot ulcer treated with laser/phototherapy	Process
B.7b	Proportion of people with a non-healing diabetic foot ulcer treated with extracorporeal shockwave therapy	Process
B.7c	Proportion of people with a non-healing diabetic foot ulcer treated with ultrasound therapy	Process
B.7d	Proportion of people with a non-healing diabetic foot ulcer treated with physical therapy other than laser, shockwave or ultrasound	Process
B.8a	Proportion of people with a non-healing diabetic foot ulcer treated with topical oxygen therapy	Process
B.8b	Proportion of people with a non-healing diabetic foot ulcer treated with ozone therapy or combined oxygen-ozone therapy	Process
B.9a	Proportion of people with a non-healing diabetic foot ulcer treated with a single nutrient supplementation	Process
B.9b	Proportion of people with a non-healing diabetic foot ulcer treated with a multi-nutrient supplementation	Process

Supplementary table 4.6.1. Continued

Domain: Wound healing interventions		
B.10a	Proportion of people with a non-healing diabetic foot ulcer treated with pharmacological agents having an action on vessels	Process
B.10b	Proportion of people with a non-healing diabetic foot ulcer treated with pharmacological agents having an action on immunity	Process
B.11a	Proportion of people with a non-healing diabetic foot ulcer treated with biological debridement	Process
B.11b	Proportion of people with a non-healing diabetic foot ulcer treated with enzymatic debridement	Process
B.12a	Proportion of people with a non-healing diabetic foot ulcer treated with amputation	Process
B.12b	Proportion of people with a non-healing diabetic foot ulcer treated with bony surgical offloading	Process
B.12c	Proportion of people with a non-healing diabetic foot ulcer treated with soft tissue surgical offloading	Process
Domain: Peripheral artery disease (PAD)		
C.1a	Proportion of people with a diabetic foot ulcer and inadequate perfusion treated with endovascular surgery	Process
C.1b	Proportion of people with a diabetic foot ulcer and inadequate perfusion treated with open vascular surgery	Process
C.1c	Proportion of people with a diabetic foot ulcer and inadequate perfusion undergoing revascularization based on the angiosome concept	Process
Domain: Offloading		
D.1	Proportion of people with a non-infected, non-ischemic plantar neuropathic diabetic foot ulcer treated with a non-removable knee-high offloading device	Process
D.2	Proportion of people with a non-infected, non-ischemic plantar neuropathic diabetic foot ulcer treated with a knee-high offloading device	Process
Domain: Secondary prevention		
E.1	Proportion of people with a (history of) diabetic foot ulcer receiving patient education	Process
E.2a	Proportion of people with a history of peripheral neuropathy (PNP) receiving therapeutic footwear and/or custom-made insoles, or custom-made shoes	Process
E.2b	Proportion of people with a history of diabetic foot ulcer receiving optimization by plantar pressure measurements of their custom-made footwear and/or insoles	Process
E.3	Proportion of people with a (history of) diabetic foot ulcer treated within the context of a prevention management programme for diabetic foot	Process

[a] umbrella indicator = unifying indicator under which the specific and related interventions was grouped and which allows to assess the delivery of such therapy regardless the type
[b] honey derivatives, silver or antibiotics

Supplementary table 4.6.2. List of inappropriate indicators

No.	Indicator	Indicator type
Domain: Organization of care		
A.4	Proportion of diabetic foot clinics that participate to a pay-for-performance programme	Structure
Domain: Wound healing interventions		
B.3	Proportion of people with a non-healing diabetic foot ulcer treated with isolated cellular therapy	Process
B.5	Proportion of people with a non-healing diabetic foot ulcer treated with isolated growth factor	Process
B.7b	Proportion of people with a non-healing diabetic foot ulcer treated with extracorporeal shockwave therapy	Process
B.7c	Proportion of people with a non-healing diabetic foot ulcer treated with ultrasound therapy	Process
B.7d	Proportion of people with a non-healing diabetic foot ulcer treated with physical therapy other than laser, shockwave or ultrasound	Process
B.8a	Proportion of people with a non-healing diabetic foot ulcer treated with topical oxygen therapy	Process
B.8b	Proportion of people with a non-healing diabetic foot ulcer treated with ozone therapy or combined oxygen-ozone therapy	Process

Supplementary table 4.6.3. List of indicators for which a collective opinion could not be reached

No.	Indicator	Indicator type
Domain: Organization of care		
A.5	Proportion of people with a diabetic foot ulcer receiving nurse-led care	Structure
Domain: Wound healing interventions		
B.4	Proportion of people with a diabetic foot ulcer treated with systemic hyperbaric oxygen therapy	Process
B.7a	Proportion of people with a non-healing diabetic foot ulcer treated with laser/phototherapy	Process
B.10b	Proportion of people with a non-healing diabetic foot ulcer treated with pharmacological agents having an action on immunity	Process
B.11a	Proportion of people with a non-healing diabetic foot ulcer treated with biological debridement	Process
B.11b	Proportion of people with a non-healing diabetic foot ulcer treated with enzymatic debridement	Process
Domain: Offloading		
D.2	Proportion of people with a non-infected, non-ischemic plantar neuropathic diabetic foot ulcer treated with a knee-high offloading device	Process

Chapter 5

BOTTOM-UP APPROACH TO BUILD A ‘PRECISION’ RISK FACTOR CLASSIFICATION FOR DIABETIC FOOT ULCER HEALING. PROOF-OF-CONCEPT

This chapter is based on:
Flora Mbela Lusendi, Giovanni Arnoldo Matricali, An-Sofie Vanherwegen, Kris Doggen and Frank Nobels. “Bottom-up Approach to Build a ‘Precision’ Risk Factor Classification for Diabetic Foot Ulcer Healing. Proof-of-Concept.” *Diabetes Research and Clinical Practice* 191 (September 2022): 110028. https://doi.org/10.1016/j.diabres.2022.110028

5.1 Abstract

Background: DFU have a complex multifactorial pathophysiology. It is crucial to identify essential prognostic variables to streamline therapeutic actions and quality-of-care audits. Although SINBAD and University of Texas (UT), the most frequently used prognostic classification systems, were prospectively, validated, not all individual parameters were shown to have consistent associations with healing. In this study, we used a bottom-up approach relying on robust methods to identify independent predictors of DFU healing.

Methods: 1,664 DFU patients were included by 34 Belgian DFCs. Twenty-one patient- and foot-related characteristics were recorded at presentation. Predictors of healing were identified using multivariable Cox proportional hazard regression. Multivariable models were built using backward regression with multiple imputation of missing values and bootstrapping.

Results: Five essential independent variables were identified: presentation delay, history of minor amputation, ulcer location, surface area and ischemia. This five variable-model showed a better performance compared to models based on existing classification systems.

Conclusions: A bottom-up approach was used to build a prognostic classification for DFU healing based on large databases. It offers new insights and allows to tailor the classification to certain clinical settings. These five parameters could be used as a ‘precision classification’ for specialized DFCs.

Keywords: classification, diabetic foot, prediction model, quality improvement, wound healing

5.2 Introduction

DFU is commonly encountered in people with diabetes.[201] Over their lifetime, approximately 25% of people with diabetes develop one or more episodes of DFU which can lead to long periods of disability and to lower-limb amputation [152]. It is widely recognized that treatment requires an intensive multidisciplinary approach [193,194] and represents substantial healthcare costs [80,202]. In addition, the health status and quality of life of patients with a DFU are significantly impacted [66]. Consequently, DFU constitutes a major burden for the individual as well as for society.

The multifactorial pathophysiology of DFU makes its understanding and management complex. While detailed descriptions of the foot problem are often recorded in clinical files, it is crucial to identify the essential variables which influence DFU outcomes in order to facilitate communication in the care team, to streamline therapeutic actions, and to organize quality-of-care audits [203].

Numerous classification systems that try to capture the essential prognostic elements have been published [29,30]. The two classifications most commonly used in clinical practice are the Site, Ischemia, Neuropathy, Bacterial infection, Area, and Depth (SINBAD) and the University of Texas (UT) scores. Recently, the SINBAD score has been endorsed by the International Working Group on the Diabetic Foot [204].

However, these existing classifications were developed using “top-down” approach including variables that are considered essential by clinicians experienced in DFU care, based on pathophysiological insights. These variables include: ulcer characteristics (area, depth, location), loss of protective sensation (LOPS), peripheral artery disease (PAD) and infection [30,205–208].

SINBAD originates from S(AD)SAD that used ulcer area, depth, sepsis, arteriopathy and denervation as components [203]. The prospective validation of S(AD)SAD carried out by Treece *et al*. revealed that only area, depth and arteriopathy contributed independently to non-healing of DFU [209]. However, when creating SINBAD all elements of S(AD)SAD were retained and ulcer site was added, because it was also considered to be an important determinant of outcome.

The six elements are scored separately as 0 (absent) or 1 (present) and a total score is calculated across the six elements. The modified system was validated in an international study in which data from four centres were used to evaluate the association between each SINBAD baseline variable and healing. Elements most consistently associated with healing were ischemia, infection and ulcer depth [33].

The UT system is leaner and classifies DFUs using a binomial matrix, according to depth (grade 0, 1, 2, 3) and presence of infection (stage B), ischemia (stage C), or both (stage D) without providing an integrated unified score. A recent large observational comparison, in a real-world clinical setting, demonstrated that the UT and SINBAD scores had similar prognostic ability for predicting foot ulcer outcomes [210]. These findings suggest that the SINBAD system includes elements that may be less essential.

On the other hand, because the UT and the SINBAD systems were developed through expert opinion, some important factors in predicting DFU outcomes might be missing.

Therefore, there is a need to adopt a bottom-up approach using large data sources and accurate methods to investigate the influence of different factors on DFU outcomes. In this study, we used a prospective nation-wide database to identify and validate independent predictors of DFU healing to guide clinical risk assessment and to allow evaluation and improvement of quality of care.

5.3 Methods

Study design and population

We used data prospectively collected by the recognized Belgian multidisciplinary DFCs during the audit-feedback quality improvement initiative named “IQED-Foot”. IQED-Foot is organized by Sciensano, the Belgian Scientific Institute of Public Health. Details of the audit-feedback initiative have been described previously [143,211]. IQED-Foot has the permission of the Information Security Comity to collect and use patient data. All data were pseudonymized by a trusted third party. As the data are not anonymous, the data are not publically available.

In summary, data from IQED-Foot audits 4 (organized from September 2013 to March 2015) and 5 (organized from January 2016 to July 2017) were used. During the first three audits, the questionnaire was fine-tuned with the aim of avoiding misinterpretations and improving data quality [143]. Audits 4 and 5 were designed as prospective follow-up studies with a 1-year period during which each DFC included the first 52 patients with a new diabetic foot problem [212].

Patients were followed up until healing or to a maximum of 6 months. All wounds were ulcers that penetrated deep into or through the skin (not a superficial abrasion or blister). Patients only suffering from active Charcot were excluded from this study.

Baseline parameters and outcomes

DFCs were asked to record data through a standardized electronic questionnaire. The following data were recorded at inclusion: age, gender, diabetes mellitus type, diabetes diagnosis date, smoking status and presence of ipsilateral and/or contralateral DFUs. The medical history was recorded for history of renal disease, cardiovascular disease, any open surgery or endovascular treatments on the lower-limb arteries, DFU, and minor and major amputation. Data on referral was recorded, i.e. whether the patient was referred by a healthcare professional or presented at his own initiative. In addition, presentation delay was recorded, defined as “the number of weeks the foot problem existed before the first consultation in the DFC”. DFU severity was assessed according to the PEDIS [32] classification system (a very detailed classification used for research purposes). Ischemia was defined as no palpable pulses, ankle-brachial index (ABI) < 0.9, toe-brachial index (TBI) ≤ 0.6 or transcutaneous oxygen pressure (TcPO2) < 60 mmHg. The location was categorized as toes, dorsum, heel, plantar midfoot and plantar forefoot. DFU healing was recorded, defined as complete epithelialization with or without minor amputation (amputation below the ankle).

Statistical analysis

Descriptive statistics included mean ± standard error (SE) or median, and 25th and 75th percentiles. Survival analyses were carried out to study the association of baseline parameters with DFU healing (details in *Model building strategy*). Time to healing was calculated from the date of the first consultation to the date of healing, if known, or to the date of last consultation (within the 6 month follow-up period) when unknown (one case in audit 4 and one case in audit 5). For patients who died before the DFU healed or had an ulcer-related major amputation or whose healing status was unknown, the DFU was regarded as not healed. Follow-up was censored at the time of death, the time of major amputation or at the end of the observation period (184 days after inclusion). A p value < 0.05 was considered statistically significant. All statistical analyses were performed in SAS (version 9.4, SAS Institute Inc, Cary, NC, USA).

Model building strategy

Missing data were assumed to occur at random, in an arbitrary pattern. Multiple imputation by fully conditional specification was performed to handle missing values. Forty imputed datasets were created. Results across imputations were combined using Rubin's rules [213,214].

A bottom-up approach was used to develop models of predictors of DFU healing using data from audit 4 (model building audit). Patient and ulcer characteristics at presentation were selected as potential predictors.

Multivariable analyses were performed using Cox proportional hazards (PH) regression. Multivariable models were built using the method described by Heymans *et al.* [215], which aims to limit the impact of missing data and sampling variation on model building and performance. To do that, the method combines multiple imputation (described above) and bootstrapping. First, 200 bootstrap samples were generated by randomly drawing observations with replacement from each imputed data set (original data set). Thereby, the sample variation in the original data set was mimicked. Then, stepwise regression analysis was applied on each imputed data set (N = 40) and on each derived bootstrap sample. Multivariable Cox PH regression with backward regression using a p value greater than 0.157 for removal of variables was chosen [216]. For each variable, an inclusion frequency, i.e. the proportion of times (proportional to the strength of the effect) that the variable appeared in the model across imputations and bootstraps (N = 8,000), was calculated. Models were produced by keeping variables whose inclusion frequency exceeded a certain threshold. Threshold values were chosen as a function of the number of included variables. Next, model performance, i.e. the ability of the model to differentiate patients experiencing DFU healing from those which will not, was assessed by computing Harrell's c-statistic (c-index) [217]. The performance of the models issued from the original data set, named the apparent performance (AP), was calculated by averaging the performance across the 40 imputed data sets. To adjust the AP for overfitting, a correction factor (optimism) was estimated. Calculating optimism involved, first, determining the performance of models across the 200 bootstrap samples, called the bootstrap performance (BP).

The next step involved calculating the test performance (TP) obtained by applying models issued from bootstrap samples on the imputed data sets (original data set). Subsequently, the optimism was calculating by subtracting BP from TP. Lastly, the AP was corrected by subtracting the average optimism [215,218]. The internal validity of the model was addressed by bootstrapping (see above) whereas the temporal validation of the final model was addressed by applying the model on data of audit 5 (model testing audit) and calculating the AP.

5.4 Results

Study population

In the model building audit, 34 DFCs sampled 1,747 unique patients of whom 83 were lost to follow-up. Therefore, a total of 1,664 patients with a DFU were analysed. Median follow-up time was 4.7 months.

Patient and ulcer characteristics are presented in Table 5.1. Patients were mainly male (65.7%) with a median [P25-P75] diabetes duration of 14.8 [8.8 - 23.8] years. In 78.7% of patients, the ulcer already existed 3 weeks or more before the first consultation. About 24.9% of patients presented to the DFC on their own initiative. Comorbidities were frequent. The most prevalent location was toes (49.1%). Sixty-five percent of ulcers had an area ≥ 1 cm^2 among which 26.9% were located on the toes.
PAD was diagnosed for 56.1% of limbs whereas the absence of sensation was reported for 86.2% of feet. About 85.9% of ulcers extended beyond the dermis and 42.1% were infected beyond the dermis.

Predictors of DFU healing

At the end of follow-up, 54.9% of ulcers were healed and 6.3% of patients had died. The major amputation rate was 2.7%. At 6 months, the probability of DFU healing, calculated by survival analysis, was 61.5%.
The multivariable analysis is illustrated in Figure 5.1. The baseline characteristics significantly associated with adverse DFU healing are: presentation delay > 4 weeks, presence of contralateral DFUs, history of lower-limb revascularization, history of minor amputation, ulcer surface area ≥ 1 cm^2, ulcer located on plantar midfoot, dorsum or heel and presence of ischemia (subcritical or critical ischemia). On the other hand, superficial infection was independently associated with a higher probability of DFU healing (Hazard ratio (HR) > 1).

Multivariable model and performance

To obtain a model that strikes an optimal balance between parsimony and performance, variables were successively eliminated from the full model shown in table 2 by backward regression using a p value for elimination from the model of 0.157. The inclusion frequency of predictors by applying a p value of 0.157 are shown in Supplementary table 5.7.1.

Table 5.2 summarizes the performance of the multivariable models. It presents the AP of the original model and the corrected AP. The performance of the model including all 21 predictors (full model) was 0.675. After correcting for optimism, performance was 0.665. Successive elimination of variables from the model, by raising the inclusion frequency threshold, resulted in a slight decrease in model performance. The model including the 5 most frequently selected variables in the models achieved a corrected performance of 0.658. These variables were ulcer location, presentation delay, history of minor amputation, ulcer surface area and ischemia (Table 5.3).

Next, we addressed the performance of the models on the model testing audit (N=1,762). As expected, the performance was lower than in the model building audit, but the differences were generally small (c-index of 0.640). Finally, the performance of models based on the ulcer classification systems PEDIS, SINBAD and UT were calculated using the model building audit data. The model based on the SINBAD classification, consisting of six variables showed a c-index of 0.614, which was inferior to the performance of our model of 5 variables. The c-index was 0.616 for the model based on PEDIS (5 variables), 0.527 for UT grade (depth) and 0.569 for UT stage (ischemia/infection).

Table 5.1. Patient and ulcer characteristics of patients eligible for outcome analyses (N=1,664)

	% Missing	n (%)
Sex, men	0	1,107 (65.7)
Age	0	
< 61 years		413 (24.5)
61-69 years		443 (26.3)
> 69-78 years		379 (22.5)
> 78 years		450 (26.7)
Diabetes duration	23.9	
< 8 years		303 (23.6)
8-14 years		302 (23.5)
> 14-23 years		328 (25.5)
> 23 years		351 (27.4)
Diabetes mellitus type	0.7	
Type 1		124 (7.4)
Type 2		1,525 (91.0)
Other		25 (1.5)
Smoking habits	3.1	
Never		808 (49.5)
Quit		538 (32.9)
Current		288 (17.6)
Presentation delay	5.7	
≤ 2 weeks		336 (21.2)
3 - 4 weeks		491 (30.9)
5 - 8 weeks		367 (23.1)
≥ 9 weeks		392 (24.7)
Presentation on patient's initiative	2.1	419 (24.9)
Additional ipsilateral DFUs	1.1	467 (28.1)
Contralateral DFUs	1.8	303 (18.3)
History of cardiovascular disease[a]	0.7	595 (35.6)
History of renal disease[b]	2.1	559 (33.8)

Table 5.1. Continued

	% Missing	n (%)
History of lower-limb revascularization	0.7	511 (30.5)
History of diabetic foot ulcer	1.1	1,142 (68.5)
History of minor amputation[c]	0.7	452 (27.0)
History of major amputation[d]	2.6	70 (4.3)
Ulcer Surface area	2.1	
< 1 cm²		572 (34.7)
≥ 1 cm² and < 3 cm²		717 (43.4)
≥ 3 cm²		361 (21.9)
Ischemia (PAD)	2.0	
No PAD		726 (43.9)
Subcritical ischemia		711 (43.0)
Critical ischemia		216 (13.1)
Depth	0.9	
Superficial		236 (14.2)
Deep (beyond dermis)		919 (55.0)
Probe to bone		515 (30.9)
Infection	1.5	
No infection		425 (25.6)
Superficial infection		534 (32.2)
Deep infection (beyond dermis)		626 (37.7)
Systemic infection		73 (4.4)
Loss of protective sensation	2.2	1,422 (86.2)
Location	0.2	
Toes		821 (49.1)
Plantar forefoot		183 (11.0)
Plantar midfoot		332 (19.9)
Dorsum		79 (4.8)
Heel		254 (15.2)

[a]Defined as stroke, transient ischemic attacks, myocardial infarction, percutaneous coronary intervention and coronary artery bypass surgery.
[b]Defined as either (1) MDRD (Modification of Diet in Renal Disease) eGFR (estimated glomerular filtration rate) < 50 ml/min and/or creatinemia > 1.5 mg/dl or (2) end-stage renal disease (ESRD) defined as a history of renal transplantation, or current dialysis and/or peritoneal dialysis.
[c]Defined as amputation where heel support is still possible.
[d]Defined as amputation where heel support is no longer possible.
PAD: peripheral artery disease.

Table 5.2. Performance of multivariable models developed based on a methodology combining multiple imputation, bootstrapping and backward regression

Threshold	n	Model building audit		Model testing audit
		Apparent performance	Corrected apparent performance	Performance
99%	2	0.607	0.608	0.595
98%	5	0.655	0.658	0.640
75%	7	0.662	0.658	0.652
60%	10	0.666	0.661	0.660
0% (full model)	21	0.675	0.665	0.667

Threshold: minimum number of times (in percentage) that a variable must appear across imputations and bootstraps to be selected.
n: number of variables included in the multivariable model.
Apparent performance: performance of models issued from imputed data sets.
Bootstrap performance: calculated across the 200 bootstrap samples to estimate correction factor.

Table 5.3. Essential prognostic elements derived from our models

Presentation delay	P	> 4 weeks
Amputation history	A	previous minor amputation
Site	S	midfoot, dorsum, heel
Area	A	≥ 1 cm²
Ischemia	I	no palpable pulses, ABI < 0.9, TBI ≤ 0.6 or TcPO2 < 60 mmHg

ABI: Ankle-brachial index, TBI: Toe-brachial index, TcPO2: Transcutaneous oxygen pressure

Figure 5.1. Multivariable analysis of baseline characteristics associated with DFU healing probability
The association between baseline characteristics and DFU healing was analysed in a multivariable model. The hazard ratio (HR) of DFU healing for each variable is shown on the right. Statistically significant (P < 0.05) factors associated with lower likelihood to heal are highlighted in red, while statistically significant factors associated with higher likelihood to heal are highlighted in green. Variables that were found not to be significant (P ≥ 0.05) are in gray.

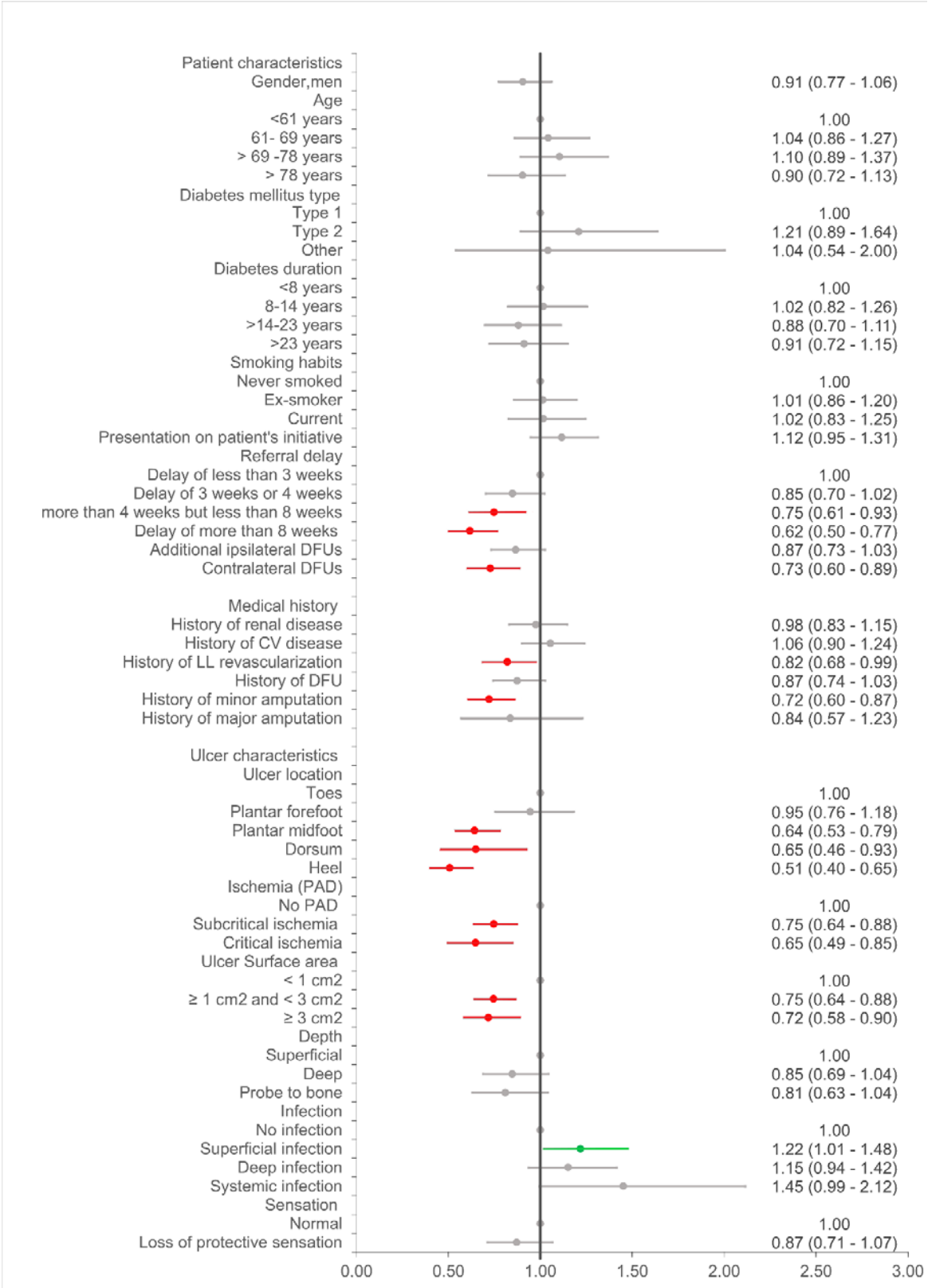

Figure 5.1. Multivariable analysis of baseline characteristics associated with DFU healing probability. The association between baseline characteristics and DFU healing was analysed in a multivariable model. The hazard ratio (HR) of DFU healing for each variable is shown on the right. Statistically significant ($P < 0.05$) factors associated with lower likelihood to heal are highlighted in red, while statistically significant factors associated with higher likelihood to heal are highlighted in green. Variables that were found not to be significant ($P \geq 0.05$) are in gray.

5.5 Discussion

In this study, we used a bottom-up approach to build a risk factor classification for DFU healing, based on prospectively collected patient and ulcer characteristics at presentation in Belgian DFCs We developed and validated multivariable models that can be used for risk stratification systems or quality-of-care audits.

Among the 21 potential predictors that we reported, five elements were identified as essential prognostic elements: ulcer location (midfoot, dorsum and heel), presentation delay, history of minor amputation, ulcer surface area, and ischemia (Table 3).

Our results showed that ulcer location (midfoot, dorsum and heel), ulcer surface area ≥ 1 cm^2 and ischemia were strong determinants of non-healing. This is consistent with SINBAD and numerous previous studies [25,206,208,219,220].

The absence of sensation did not show a significant relationship with DFU healing in multivariable analysis. Previous studies conducted by Treece *et al.* [209] and Ince *et al.* [33] also showed that LOPS is not a strong determinant of non-healing. LOPS represents an important factor in the pathogenesis of DFU and should therefore be considered when assessing the risk of developing a DFU in a person with diabetes. However, it does not seem to contribute to the prediction of healing of a DFU, at least in DFCs where offloading is the standard of care.

Despite its validation in S(AD)SAD, its use in SINBAD and UT, no multivariable association was found between depth and DFU healing in the present study. This may be explained by the presence of strong determinants such as ischemia, which overshadow the importance of ulcer depth.

Presence of superficial infection unexpectantly showed a significant positive association with DFU healing in multivariable analysis. These results may be related to the presence of other factors in our multivariable model, to other unmeasured factors (which are predictive of better DFU healing and are correlated with the presence of infection), to a more rapid healing of infected ulcers thanks to a more aggressive treatment, and finally to the large proportion of DFU on toes in the current study, for which infection can be treated by amputation of the toe, thus resulting in rapid resolution of the infected DFU. Moreover, infection is usually easily treatable with debridement and antibiotics in patients with good arterial circulation, which emphasizes the essential prognostic role of ischemia.

Our study also revealed additional strong determinants of non-healing. We found that longer presentation delay was significantly associated with non-DFU healing, similarly to what Smith-StrØm *et al.* [221] and Margolis *et al.* [222] have reported. Although definitions were different, these results highlight the importance of early detection and treatment. We also observed a significant relationship between DFU healing and history of minor amputation, which is not commonly reported in the literature. Zadeh *et al.* [223] noted a lack of association between history of amputation and DFU healing without making the distinction between minor amputations and major amputations. The clinical importance of previous minor amputation may be related to the fact that it leaves less room for debridement and for maintaining a ‘shoeable’ foot.

The model that we propose as striking the best balance between parsimony and performance contains 5 variables that seem feasible for data collection. Our five-variable model achieved a higher performance compared to models based on existing classification systems but it was similar to the general prognostic performance of SINBAD and UT reported by Leese *et al.* [210]. This may be attributed to the fact that a model usually behaves best (best c-statistic or model fit) in the population from which the model was derived. Nevertheless, our model identified blind spots in existing systems. None of the assessed classification systems includes presentation delay and history of minor amputation. Compared to variables in many existing classification systems, our model was developed from a large and heterogeneous set of variables, using a robust modelling strategy. By using a bottom-up approach, we were able to identify models which explain more variation (i.e. have better performance) than models of equal size, but developed using a conceptual framework (i.e. focusing on specific aspects such as ulcer characteristics).

Our models were developed based on data prospectively collected from more than 30 Belgian DFCs, without selecting referral centres, making the study generalizable. We used a large study population with DFU beyond the dermis. The care delivered to the patients showed variation with regard to key management strategies [143]. This difference in treatment could have been captured by introducing treatment related-variables in the model like in the bottom-up study performed by Zhang *et al*. [224]. By doing so, however, we would have been inconsistent with the goal of this study to develop a risk classification system, which by definition is applied before treatment starts.

The main limitation of our study is that it was performed in a specific setting of well-organized Belgian DFC's clinics with high standards of care and a long history of participation to quality assurance. Other parameters might be more important in other settings. In the main validation paper of SINBAD [33], two centres from Europe, one from Africa and one from the Far East were included and a clear inconsistency in the importance of the individual elements of SINBAD was observed between these regions. This limitation of our study can however also be a strength. In an era of precision medicine, it can indeed be important to use large local databases for the bottom-up creation of a local risk factor classification – a precision classification – allowing tailoring of prognostic classifications to parameters that are really important for that specific setting. One could even go further and make a separate prognostic classification for DFU at the toes and at other sites of the foot, since it is apparent that the prognosis is different.

We expect that our predictor variables will be translatable, after external validation, to other geographical DFU populations in similar settings of well-organized DFCs. The five variables that have been identified through the current proof-of-concept study are easy to collect and are often already assessed routinely from all patients that present with a DFU to determine the best treatment strategy. Moreover, one of the cornerstones of this concept of a precision classification is the ability to tailor it towards the local needs, based on the available clinical data.

5.6 Conclusions

Based on a robust methodology, this study identified a five-variable model, striking an optimal balance between data collection burden and performance. The five variables are presentation delay, amputation history, site, area and ischemia (PASAI). It is a proof-of-concept that a bottom-up approach can be used to build a risk classification system for DFU healing based on existing databases. This approach can on the one hand eliminate non-essential parameters of existing classifications and on the other hand add other parameters that were previously not envisioned. It can also tailor prognostic classifications to parameters that are really important for that specific setting. PASAI could be used as a ‘precision classification’ for specialized DFCs, if future prospective validation confirms its robustness.

5.7 Supplementary figures and tables

Supplementary table 5.7.1. Inclusion frequency and ranking for each variable selected by backward regression in the 8,000 bootstrap samples using a p value of 0.157

	Ranking	%
Ulcer location	1	100
Presentation delay	2	99.5
Ischemia (PAD)	3	99.0
Surface area of ulcer	4	98.2
History of minor amputation	5	98.0
Contralateral DFUs	6	94.9
History of lower-limb revascularization	7	76.8
Infection of ulcer	8	70.7
History of DFU	9	64.9
Additional ipsilateral DFUs	10	61.2
Ulcer depth	11	56.7
Age	12	54.9
Diabetes duration	13	54.5
Loss of protective sensation	14	51.1
Presentation on patient's initiative	15	46.3
Diabetes mellitus type	16	43.4
Sex	17	40.5
History of major amputation	18	32.5
Cardiovascular history	19	24.5
Smoking	20	20.8
History of renal disease	21	19.9

DFU: diabetic foot ulcer, PAD: peripheral artery disease.
Ranking: rank of the inclusion frequencies.
Inclusion frequency (%): the percentage of models across the 8,000 bootstrap samples that included the given variable.

Chapter 6

ASSESSING PATIENT-REPORTED OUTCOME MEASUREMENTS, POTENTIAL SOURCE OF QUALITY INDICATORS

This chapter is partially based on:
Wahid Rezaie, Flora Mbela Lusendi, Kris Doggen, Giovanni A. Matricali, and Frank Nobels. Health-related quality of life in patients with diabetic foot ulceration: study protocol for adaptation and validation of patient-reported outcome measurements (PROMs) in Dutch-speaking patients. BMJ Open. 2019 Dec 23;9(12):e034491

6.1 Abstract

Background: DFU is a common late-stage complication of diabetes with negative consequences for the functional, psychological and socio-economic status, and therefore the patient HRQoL. Patient-reported outcomes measures (PROMs) can be used to gather information about patient HRQoL. This information may serve to determine treatment strategy and drive quality of care improvement. Measurement properties of a PROM should be assessed, using consensus-based standards (COSMIN), and considered adequate before its use in clinical practice. The Diabetic Foot Scale-Short Form (DFS-SF) and the Lower Extremity Functional Scale (LEFS) are PROMs designed respectively for measuring HRQoL among DFU patients and physical functioning in patients with lower extremity disorders. However, their psychometric qualities need to be evaluated in Belgian Dutch-speaking patients with DFU.

Aim: The aim of this study is to assess the measurement properties related to the domain of reliability of the DFS-SF and LEFS questionnaires for Belgian Dutch-speaking patients with DFU, as a first step to start assessment of the domains validity and responsiveness.

Methods: A monocentric, observational cohort study was conducted. Belgian-Dutch versions of the DFS-SF and LEFS, adapted from the Netherlands Dutch versions, were used. After the cultural adaptation, which consisted in minor linguistic changes to make the instruments understandable and relevant for Belgian Dutch-speaking patients with DFU, the following measurement properties were evaluated: floor and ceiling effects, internal consistency, test-retest reliability and measurement error. Patients completed the 2 questionnaires at first contact and 3 weeks later to assess test-retest reliability and measurement error.

Results: A population of 105 patients with severe DFU were recruited for assessing both PROMs. Among them 52 patients that returned to consultation within 21 days and reported no changes in their foot condition, completed the questionnaires twice. Ceiling effects were observed for some of the DFS-SF subscales (15.2%-23.8%). Internal consistency for DFS-SF subscales (Cronbach's alphas between 0.70-0.92) and LEFS (Cronbach's alpha = 0.95) were good and comparable to other language versions. Except for the subscale bothered by ulcer care (ICC = 0.36), the DFS-SF subscales showed mostly moderate test-retest reliability ($0.58 < ICC < 0.84$) while the test-retest reliability of LEFS was good (ICC = 0.85). For both questionnaires, large variations in repeated score measurements from the same stable patients were observed.

Conclusion: This study assessed the reliability of the Belgian-Dutch DFS-SF and LEFS questionnaires. Our findings were comparable to those observed in similar studies of other language versions; however, our evaluation was more comprehensive by providing key information that is often missing in such studies. Although both questionnaires have shortcomings, they fulfilled the COSMIN criteria and are sufficient reliable for further validation. Next steps should concentrate on evaluating the measurement properties related to the domains of validity and responsiveness for evaluating emotional and physical functioning of patients with DFU.

6.2 Introduction

DFU constitutes a major disability burden encountered in persons with diabetes.[152] It is associated with high morbidity, with recurrence rates of 65% at 3-5 years and a lifetime lower extremity amputation incidence of 20%.[23] The management of DFU requires a multidisciplinary approach with intensive and prolonged treatment. Consequently, DFU not only represents major healthcare consumption and high costs,[74,80,153] but also has a significant impact on patient HRQoL, including physical, social and psychological aspects. A systematic review demonstrated significant limitations in physical activities such as walking, climbing stairs and carrying groceries among people with DFU.[66] Another study suggested that physical restrictions in daily life may significantly reduce social activities in people with DFU compared to a population of individuals without DFU.[225] Recently, a review indicated that DFUs are a source of specific emotional responses, with fear of amputation predominantly present.[69]

Because DFU have a significant impact on the HRQoL of people with diabetes, the use of PROMs considering aspects as physical and social limitations, pain, or depression is important. PROMs are self-administered questionnaires designed to collect PROs, defined as any aspect of a patient's health status that is assessed directly by the patient without the interpretation of the patient's response by anyone other than the patient.[226] This information about the patient health status helps to predict treatment success and may assist to determine a multidisciplinary treatment strategy that does not only consider clinical factors, but also takes the patient's perspective into account.[227] In addition, PROs may also be used, along with the clinical outcomes, to provide guidance on quality improvement in the context of quality of care assessment across hospitals.[228] In the UK, the national quality initiative for accreditation and auditing of diabetic foot services collects PROs, using a generic questionnaire (EQ5D-3L).[146] In contrast, at the moment, the Belgian nationwide quality improvement initiative, named "IQED-Foot" does not include HRQoL data.[143,211]

PROs can be measured by using generic or disease-specific instruments. Before a PROM can be routinely used in clinical practice, its quality, reflected by its measurement properties, should be assessed and considered adequate according to the standards defined by the COSMIN group.[229] The COSMIN group distinguished three quality domains, each containing one or more measurement properties, as illustrated in the taxonomy they provided (Figure 6.1).[230,231] Validity encompasses three forms: content validity, construct validity and criterion validity. Responsiveness has been defined as the ability of a questionnaire to detect clinically important changes over time even if these changes are small. Reliability concerns the degree to which repeated measurements taken by the instrument in stable persons provide similar answers, including internal consistency, test-retest reliability and measurement error.

According to a previous agreement, internal consistency would be included in the domain reliability, even though it refers to the quality of the scale at the item level, rather than as a whole.[230]

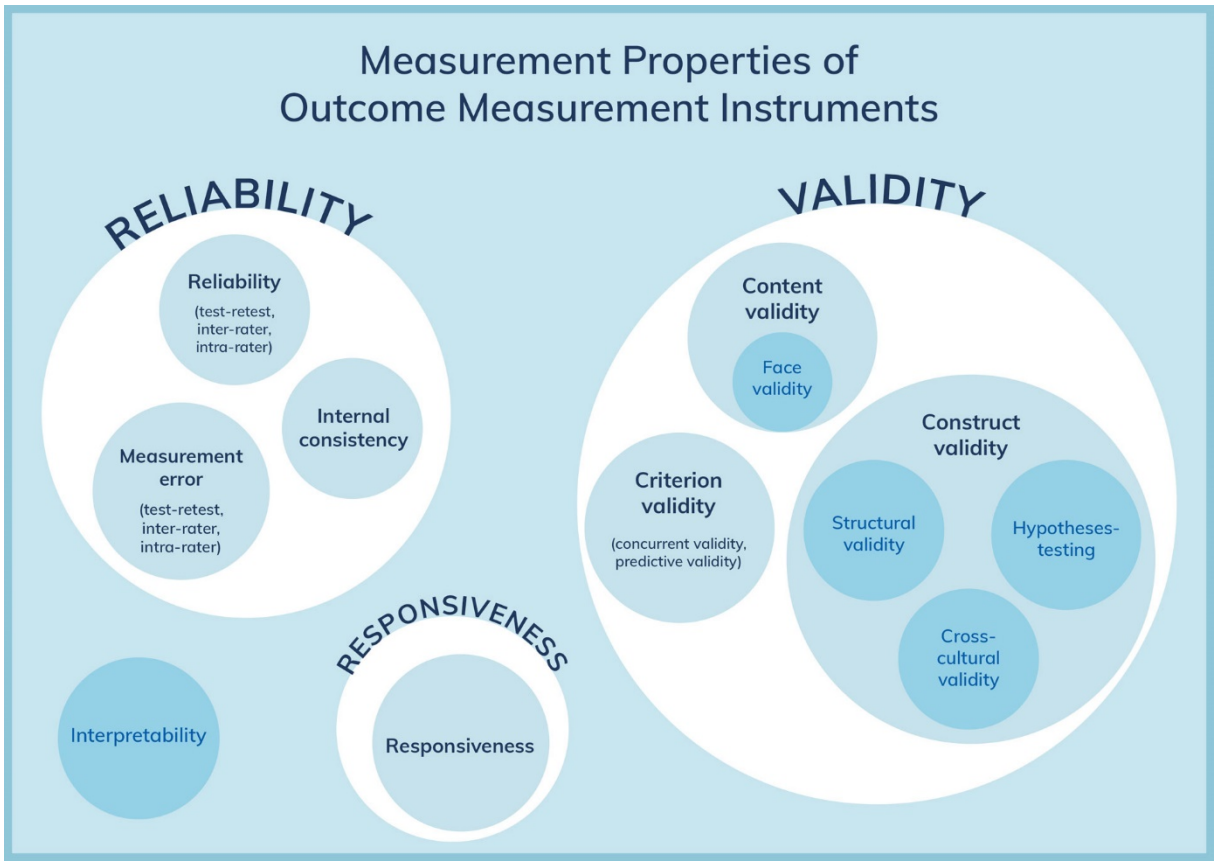

Figure 6.1. Measurement properties defined by the COSMIN group and classified in 3 domains. Figure adopted from Mokkink *et al*.[230]

Scores of PROMs can be influenced by many factors (so-called sources of variation), such as the time or occasion when the measurement was taken, the instructions that were given to patients, the type of device or the settings that were used.[232,233] Reliability studies help to estimate the influence of different sources of variation on measurements and scores, in two ways.[234] Firstly, by examining different forms of reliability, such as test-retest reliability, to determine which sources of variation are most distorting the measurement.[233] Secondly, by examining measurement error to determine the absolute amount of error in the scores due to the aforementioned sources of variation.[235] Improving the standardization of these sources of variation can enhance the accuracy of measurements, resulting in smaller errors and reducing the number of patients required for intervention studies.[236] Alongside validity, reliability and responsiveness, interpretability, defined as the degree to which one can assign qualitative meaning to the PROM's quantitative scores or changes in score, represents an important aspect of a PROM as well. It can be evaluated by providing, for instance, the percentage of missing items or the floor and ceiling effects.[229] This information is necessary for interpreting certain measurement properties and may reveal score clustering.[237]

Several instruments are being used for measuring PROs for DFU, but in many cases their measurement properties have been insufficiently studied and reported.[238–240] Compared to generic instruments, disease-specific instruments include more clinical aspects of a disease and are more sensitive to changes related to the disease. The most frequently used disease-specific instrument for measuring HRQoL among diabetic foot patients is the Diabetic Foot Ulcer Scale (DFS).
This instrument was developed by using semi-structured interviews and focus groups of patients with DFUs and their caregivers.[241] It has shown internal consistency, reliability, validity and responsiveness to wound severity and healing. A shortened version,[242] the DFS Short Form (DFS-SF), showed similar robustness and responsiveness compared with its longer version and is with 29 questions a more 'user-friendly' tool for everyday clinical practice.

The DFS-SF consists of six conceptual domains or subscales: leisure (5 items), physical health (5 items), dependence/daily life (5 items), negative emotions (6 items), worried about ulcers/feet (4 items) and bothered by ulcer care (4 items). Each item is measured by a 5-point Likert rating scale ranging from 1 "not at all" or "none of the time" to 5 "a great deal" or "all of the time" or "extremely". Domain scores are based on the sum of all items associated with that domain. The original English DFS-SF version was translated into several languages, including Chinese,[243] Greek,[244] Polish,[245] Korean,[246] Spanish,[247] Turkish[248] and Persian,[249] and was subsequently used in several quality-of-life studies.[250–252]

However, the measurement properties of DFS-SF throughout those versions, have not yet been studied and reported across all the relevant dimensions reported by the COSMIN group.[230,231] With respect to its reliability, internal consistency was predominantly reported, but the other aspects were not fully documented.[240] In addition, despite that a Dutch translation of DFS-SF for the Netherlands has undergone a full linguistic process according to a recognized methodology of translation,[253] the measurement properties of this questionnaire have not yet been evaluated in a Belgian Dutch-speaking population with DFU. Moreover, in accordance with the guidelines for cross-cultural adaptation of self-report measures proposed by Guillemin and Beaton, a cultural adaptation is needed when administering a questionnaire in a different culture and country but in the same language.[254]
Furthermore, it has been consistently advocated that HRQoL outcomes like physical function and pain should be measured independently.[255,256] Unlike other instruments,[257] the Lower Extremity Functional Scale (LEFS) is a dimension-specific instrument that can differentiate pain and physical functioning in a wide variety of disorders.[258,259] It consists of 20 items,[259] which are rated on a 4-point scale, from 0 "extreme difficulty/unable to perform activity" to 4 "no difficulty". The total maximum possible score of LEFS is 80 points, indicating very high function. The total minimum possible score is 0 points, indicating very low function.[259] The questionnaire is validated in several languages,[260,261] including in Netherlands-Dutch for patients with osteoarthritis.[262] However, the LEFS is not yet validated for assessing functional impairment of foot and ankle in diabetic foot conditions.

Given that HRQoL is adversely affected by DFU and valid and reliable measurement instruments are missing to capture PROs among people with DFU in Belgian diabetic foot services, this study aimed to assess the measurement properties of the DFS-SF and LEFS questionnaires related to the domain of reliability among Belgian Dutch-speaking patients with DFU. The first part of the study consisted of culturally adapting the Netherlands-Dutch DFS-SF and LEFS questionnaires for Belgian Dutch-speaking patients with DFU. In a second step, we evaluated their reliability and interpretability. Therefore, in the framework of this doctoral thesis, we assessed the following measurement properties: floor and ceiling effects, internal consistency, test-retest reliability, and measurement error.

6.3 Methods

Study design and population

The study was conducted as a monocentric observational cohort study in OLV Aalst Hospital (Aalst, Belgium). Participants were all consecutive patients attending the multidisciplinary outpatient DFC or being admitted to the OLV inpatient diabetic foot department, and who met the following inclusion criteria: adult persons ≥ 18 years old, adequate comprehension of the Dutch language in order to understand the questionnaires, having a severe DFU (Wagner ≥ 2), and able to provide written informed consent. The exclusion criteria were as follows: patient not able to ambulate prior to DFU (i.e., bedridden or wheelchair-dependent), cognitive dysfunction (which hampers the understanding of questionnaires), patients who underwent foot surgery or revascularization of the leg in the defined time interval. In order to preserve the study population anonymity, the subject's name or other patient identifiers were stored separately (site file) from their research data and replaced with a unique code to create a new identity for the patient.
The study protocol was approved by the Medical Ethics Committee of OLV Aalst Hospital (Belgian registration number B126201836509).

Cultural adaptation

The cultural adaptation process was derived from previous examples in the literature[263] and consisted of the following steps: a team of diabetes nurse educators with experience in caring for DFU patients reviewed the intelligibility of the questionnaires and suggested changes in consultation with patients.. This team convened with the researchers to review each individual item from the Netherlands Dutch DFS-SF and LEFS questionnaires, for making necessary language changes to produce a version that was both understandable and relevant to Belgian Dutch-speaking patients with DFU. Minor linguistic changes were made during the review process (Table 6.1), without altering the content of the questionnaires.

Then, for cognitive debriefing, the two adapted questionnaires were administered to a group of 10 patients who met the study eligibility criteria.[264] Patients were asked if they understood the questions and were able to provide answers. No ambiguities or misunderstandings of the questions were expressed by the group. Therefore, the results of these debriefing interviews were utilized to confirm the cultural relevance and clarity of each questionnaire item. As a result, a Belgian-Dutch version of DFS-SF and LEFS was finalized for further use in the current study.

Table 6.1. Adaptations made to the Netherlands-Dutch version of DFS-SF and LEFS questionnaires for Belgian Dutch-speakers.

Item	Netherlands-Dutch version	Adaptations made
DFS-SF		
2d	Pijn bij **lopen** of staan gehad?	Pijn bij **stappen** of staan gehad?
5b	De tijd die nodig is om uw voetwonde te verzorgen (zoals verband **verschonen**, op de **wijkverpleging** wachten, de wonde **schoonhouden**)?	De tijd die nodig is om uw voetwonde te verzorgen (zoals verband **vervangen**, op de **thuisverpleegkundige** wachten, de wonde **verzorgen**)?
LEFS		
1	Een **aspect** van uw gebruikelijke werk, huishouden of schoolactiviteiten	Een **onderdeel** van uw gebruikelijke werk, huishouden of schoolactiviteiten
4	**Lopen** binnenshuis	Binnenshuis **stappen**
11	250 meter **lopen**	250 meter **stappen**
12	Anderhalve kilometer **lopen**	Anderhalve kilometer **stappen**
13	Een trap op- of **aflopen** (ongeveer 10 treden)	Een trap op- of **afgaan** (ongeveer 10 treden)
16	**Hard lopen** op een vlakke ondergrond	**Lopen** op een vlakke ondergrond
17	**Hard lopen** op een oneffen ondergrond	**Lopen** op een oneffen ondergrond
18	Tijdens het **rennen** scherpe bochten maken	Tijdens het **lopen** scherpe bochten maken

PROM instrument administration and data collection

The DFS-SF and LEFS instruments were digitally administered between August 2018 and October 2021. A tablet was provided to the patient before the consultation in the waiting room. The participants were instructed on how to use the tablet and a research nurse assisted participants who found it difficult to use a tablet. In order to assess the reliability of the DFS-SF and LEFS, a time interval of 3 weeks (21 days) between the first contact (defined as baseline) and the second time completing each questionnaire was considered sufficiently short for the patient's foot condition to remain stable and sufficiently long to prevent remembrance of the answers to the first contact. Participants were asked about their subjective feeling of presence or absence of change in their foot condition before completing the questionnaire the second time. Participants who reported no change were considered stable between the two measurements and were eligible for testing the reliability of the questionnaires (interval group). Clinical data were collected from the electronic medical files based on the following variables included in IQED-Foot: age, sex, diabetes type, date of diabetes diagnosis, presence of ipsilateral and/or contralateral DFU and presence of a concurrent Charcot foot. The recorded medical histories were history of DFU, Charcot, any open vascular surgery or endovascular treatments on the lower-limb arteries and amputation (toe, minor, major). DFU severity was assessed according to the PEDIS classification system.[32] Ischemia was defined as no palpable pulses, ankle-brachial index (ABI) < 0.9, toe-brachial index (TBI) ≤ 0.6. Patients were followed for a total period of 6 months or until healing of the ulcer when this took less time.

Statistical analysis

Descriptive statistics were performed to describe the study population, the instrument scores and the number of missing values. Continuous data were reported as mean ± standard error (parametric) or median with 25th and 75th percentiles (non-parametric). Categorical data were reported as proportion. The domain scores of DFS-SF were computed based on scoring conventions previously published,[242] where all items are reverse-coded so that each domain score is ranged from 0 to 100 and higher values indicate better QoL. Missing values were addressed using complete case analysis. The Belgian-Dutch DFS-SF and LEFS questionnaires were evaluated by assessing floor and ceiling effects, internal consistency, test-retest reliability and measurement error. First survey and 3 weeks follow-up visit ratings were compared for test-retest reliability and measurement error. The adequacy of the above mentioned measurement properties were assessed using predefined criteria.[231,265,266] A p-value < 0.05 was considered statistically significant and 95% confidence intervals (CI) were provided where appropriate. All statistical analysis were performed in SAS (version 9.4. SAS Institute Inc. Cary. NC. USA).

Measurement properties

Floor and ceiling effects

Floor and ceiling effects were determined by calculating the number of individuals who obtained the lowest (floor) or highest (ceiling) possible scores. If floor and ceiling effects are present, it is likely that extreme items are missing in the lower or upper end of the scale, indicating limited content validity. As a consequence, patients with the lowest or highest possible score cannot be distinguished from each other, thus reliability is reduced. Floor and ceiling effects were considered present if more than 15% of the respondents achieved the lowest or highest score in a sample size of at least 50 patients.[231]

Internal consistency

Internal consistency is defined as the extent to which items in a questionnaire subscales are intercorrelated, thus measuring the same construct (indicator for homogeneity).[231] The correlation between items from DFS-SF and LEFS were evaluated by calculating the Cronbach's alpha and 95% CI for every subscale[235] at baseline. Internal consistency was considered good if the value for Cronbach's alpha lies between 0.70 and 0.95, calculated with an adequate number of subjects[231,266] and provided that the scale is unidimensional.

Test-retest reliability

Test-retest reliability reflects variation in measurement taken by an instrument on the same subject under the same conditions.[267] The test-retest reliability of DFS-SF and LEFS was assessed by calculating type 2,1 intraclass Correlation Coefficients (ICCs) and their 95% CI,[268] defined based on a single measurement, absolute-agreement and two-way random effects model. This form of ICC is appropriate for testing intrarater reliability with multiple scores from the same single rater.[267,269] Based on the ICC estimates and their 95% CI, test-retest reliability is considered poor when < 0.5, moderate between 0.5 and 0.75, good between 0.75 and 0.9, and excellent when > 0.90.

Measurement error

Measurement error concerns the extent to which the scores on repeated measures are close to each other,[231] in other words; how good is the agreement between repeated measurements. It illustrated the variation in the scores between both scores of a same patient (within subject/measurement). The measurement error was expressed as the Standard Error of Measurement (SEM), including systematic differences (SEM agreement). This SEM equals the square root of the error variance of an ANOVA analysis: $\sqrt{(variance\ patient + variance\ residual)}$, and was calculated using the ICC and the standard deviation (SD) as formula: SEM=SD[√1-ICC]).[237] The Bland-Altman limits of agreement (LOA) method was used to produce the SD and to plot the mean difference between two applications of the questionnaire.[270] In addition, based on SEM, we quantified the minimal detectable change at the 95% confidence level (MDC_{95}) from the formula: $MDC_{95} = SEM_{agreement} * 1.96 * \sqrt{2}$.[234] This can be interpreted as a "real" change, above measurement error.[231]

Sample size

Our sample size considerations were based on recommendations from the literature. In the context of internal consistency, rules-of-thumb vary from 4 to 10 subjects per variable, with a minimum number of 100 subjects to ensure stability of the variance–covariance matrix.[271] Regarding the number of subjects to include for assessing test-retest reliability, Giraudeau et al. reported that a sample size of 50 patients is needed to obtain a confidence interval from 0.70-0.90 around an ICC of 0.80.[272] Similarly, Terwee et al. estimated the reliability to be good if the ICC is at least 0.70 with a sample size of at least 50 patients.[231,266] According to Altman's guidelines, a sample size of at least 50 patients was judged adequate for the assessment of the agreement parameter.[273] The quality criteria for floor and ceiling effects suggest a positive rating for the absence of floor and ceiling effects if none are present in a sample size of at least 50 patients.[231] Therefore, a sample size of at least 100 patients was deemed sufficient for evaluating internal consistency provided that the scale is unidimensional, whereas a sample of at least 50 participants was considered adequate for assessing test-retest reliability and agreement.

6.4 Results

Descriptive statistics

A total of 107 patients with DFU were recruited at baseline. Clinical data were missing for 10 patients of the entire study group (9.3%). Patient and ulcer characteristics are presented in Table 6.2. Participants were predominantly male (71.1%) with a mean age of 67.7 years. The majority of patients experienced prior DFU (63.9%). Medical history of lower limb revascularization (29.9%) and toe amputation (24.7%) were also documented. About 33.3% of patients were hospitalized within 2 weeks. In total, 104 feet were examined. Forty-nine percent of ulcers had an area ≥ 1 cm^2. More than two thirds of patients (60.6%) presented with an infected ulcer. PAD was diagnosed for 31.7% of limbs whereas the absence of sensation was observed in 88.5% of feet. Among them, 52 patients (who reported no changes in their foot condition in between both questionnaire completions) completed the Belgian-Dutch DFS-SF and LEFS questionnaires twice in the required time interval of 3 weeks (21 days). No major differences were observed in patient characteristics in the interval population.

As shown in Table 3, at baseline, the highest mean DFS-SF score was observed for bothered by ulcer care whereas the lowest DFS-SF score was observed for worried about ulcers/feet. The same trend in scores was observed at 3 weeks. Compared to the score at baseline, the single score of the LEFS at 3 weeks was slightly higher. Data related to PROM questionnaires were missing for two patients at baseline (1.9%).

Table 6.2. Patient and ulcer characteristics of the study group for assessing the reliability of the DFS-SF and LEFS questionnaires

Patient Characteristics	Total population (N = 107)	Interval population (N = 52)
Observed	97*	50*
Sex, % (n)		
Male	71.1 (69)	74.0 (37)
Age (year), mean±SD	67.7±10.3	66.2±10.6
Diabetes duration (year), mean±SD	20.1±12.5	19.0±12.3
Diabetes type, % (n)		
Type 1	11.3 (11)	10.0 (5)
Type 2	83.5 (81)	86.0 (43)
Other	5.1 (3)	4.0 (2)
Concurrent Charcot disease, % (n)	0 (0/94)	0 (0)
Previous amputation, % (n)		
Toe	24.7 (24)	22.0 (11)
Minor	12.4 (12)	10.0 (5)
Major	5.2 (5)	8.0 (4)
Previous DFU, % (n)	63.9 (62)	62.0 (31)
Previous Charcot disease, % (n)	8.3 (8)	4.0 (2)
Previous revascularization LL, % (n)	29.9 (29)	30.0 (15)
Dialysis, % (n)	8.3 (8/96)	6.0 (3)
Hospitalisation within 2 weeks, % (n)	33.3 (31/93)	26.5 (13/49)
Debridement within 2 weeks, % (n)	25.8 (24/93)	18.4 (9/49)
Additional ipsilateral ulcers, % (n)	5.2 (5/96)	4.0 (2)
Contralateral ulcers, % (n)	12.5 (12/96)	8.0 (4)

Table 6.2. Continued

Foot Characteristics	104 feet*	54 feet*
Perfusion, % (n)		
No PAD	68.3 (71)	73.6 (39/53)
Subcritical ischemia	20.2 (21)	17.0 (9/53)
Critical ischemia	11.5 (12)	9.3 (5/53)
Extent (ulcer surface area), % (n)		
< 1 cm²	50.0 (52)	51.8 (28)
≥ 1 cm² and < 3 cm²	35.6 (37)	37.0 (20)
≥ 3 cm²	12.5 (13)	11.1 (6)
Depth, % (n)		
Superficial	6.7 (7)	7.5 (4/53)
Deep	56.7 (59)	58.5 (31/53)
Probe to bone	36.5 (38)	34.0 (18/53)
Infection, % (n)		
No infection	39.4 (41)	30.2 (16/53)
Superficial	23.1 (24)	34.0 (18/53)
Deep	35.6 (37)	32.1 (17/53)
Systemic	1.9 (2)	3.8 (2/53)
Sensation, % (n)		
Loss of protective sensation (LOPS)	88.5 (92)	94.3 (50/53)

*Denominator is equal to number of patients or feet mentioned here, unless specified otherwise in the specific row.

Measurement properties

Floor and ceiling effect

DSF-SF. Less than 15% of patients reported the lowest possible score (score = 0) in all subscales of the Belgian-Dutch DFS-SF. However, ceiling effects (score = 100) were observed in the subscales leisure, dependence/daily life, negative emotions and bothered by ulcer care with the highest percentage (23.8%) for dependence/daily life (Table 6.3).

LEFS. None of patients reported the lowest possible score (score = 0) and about 1.9% of patients reported the highest functional level (score = 80), implying that the Belgian-Dutch LEFS has no floor or ceiling effects (Table 6.3).

Table 6.3. Mean (± SD) scores and floor/ceiling effects (%) of the DFS-SF and LEFS questionnaires obtained from Belgian Dutch-speaking patients with DFU

	Baseline sample (n =105)				Interval group (n = 52)	
DFS-SF	Mean	SD	Floor %	Ceiling %	Mean	SD
Leisure	66.7	31.8	7.6	16.9	69.6	31.5
Physical Health	65.7	24.7	0.9	7.6	65.8	24.6
Dependence/daily life	63.5	31.2	3.8	23.8	64.5	32.1
Negative emotions	72.6	26.3	0.9	18.1	75.0	24.1
Worried about ulcers/feet	58.5	25.0	0.9	2.9	57.9	26.1
Bothered by ulcer care	79.8	17.5	0	15.2	79.9	16.8
LEFS	45.4	20.3	0	1.9	46.2	20.6

DFS-SF: Diabetic Foot Ulcer Scale Short Form; n: number; SD: Standard Deviation; LEFS: Lower Extremity Functional Scale.

Internal consistency

DSF-SF. All of the Belgian-Dutch DFS-SF subscales demonstrated good internal consistency. The values for the Cronbach's alpha ranged from 0.70 (95% CI 0.61 – 0.79) (bothered by ulcer care) to 0.92 (95% CI 0.90 – 0.95) (leisure). The internal consistency of physical health, worried about ulcers/feet, and negative emotions were not substantially improved by item deletion.

LEFS. The Belgian-Dutch LEFS showed a good internal consistency with a value for the Cronbach's alpha of 0.95 (95% CI 0.94 – 0.97) for the 20 items (Table 6.4).

Table 6.4. Internal consistency of the Belgian-Dutch DFS-SF and LEFS subscales

		Baseline sample (n = 105)	
DFS-SF	Items (n)	Cronbach's alpha	95% CI
Leisure	5	0.92	0.90 - 0.95
Physical Health	5	0.81[a]	0.76 - 0.87
Dependence/daily life	5	0.88	0.84 - 0.92
Negative emotions	6	0.90[c]	0.87 - 0.93
Worried about ulcers/feet	4	0.80[b]	0.74 - 0.86
Bothered by ulcer care	4	0.70	0.61 - 0.79
LEFS	20	0.95	0,94 - 0.97

[a]Improved from 0.8116 to 0.8152 when subscale item 4 is deleted; [b]Improved from 0.7984 to 0.8146 when subscale item 3 is deleted; [c]Improved from 0.9028 to 0.9181 when subscale item 5 is deleted

DFS-SF: Diabetic Foot Ulcer Scale Short Form; n: number; CI: confidence interval; LEFS: Lower Extremity Functional Scale.

Test-retest reliability

DSF-SF. In the interval group of patients (n = 52), the ICC values of the Belgian-Dutch DFS-SF subscales ranged from 0.36 (bothered by ulcer care) to 0.84 (dependence/daily life). All the Belgian-Dutch DFS-SF subscales showed test-retest reliability from moderate to good, except the subscale bothered by ulcer care which was found to be poor (Table 6.5).

LEFS. The ICC value of the Belgian-Dutch LEFS questionnaire was 0.85 (95% CI 0.75 – 0.91), which indicated a good level of test-retest reliability (Table 6.5).

Table 6.5. Test-retest reliability of the Belgian-Dutch DFS-SF and LEFS questionnaires using the ICC calculated in SAS by single-rating, absolute agreement, 2-way random effects model

	ICC	**95% CI**	**F test with True Value 0**			
DFS-SF			Value	df1	df2	Sig
Leisure	0.65	0.46 – 0.78	4.66	51	51	<0.0001
Physical Health	0.62	0.42 – 0.76	4.35	51	51	<0.0001
Dependence/daily life	0.84	0.75 – 0.91	11.68	51	51	<0.0001
Negative emotions	0.62	0.44 – 0.77	4.30	51	51	<0.0001
Worried about ulcers/feet	0.58	0.34 – 0.72	4.49	51	51	<0.0001
Bothered by ulcer care	0.36	0.10 – 0.57	2.1	51	51	0.0045
LEFS	0.85	0.75 – 0.91	12.3	51	51	<0.0001

DFS-SF: Diabetic Foot Ulcer Scale Short Form; ICC: Intraclass Correlation Coefficient; CI: confidence interval; LEFS: Lower Extremity Functional Scale.

Measurement error

DSF-SF. The smallest and largest SEM were observed for the leisure (2.83 points) and bothered by ulcer care (14.52 points) scales of the Belgian-Dutch DFS-SF. A minimal detectable change (MDC_{95}) of 7.84 and 40.25 were calculated, respectively, for those subscales. SEM and MDC_{95} values are reported in Table 6.6. The Bland-Altman plots showed mean differences near zero between two applications of the DFS-SF leisure and DFS-SF dependence (Figure 6.2A-2D). The largest difference was observed for the worried about ulcers/feet subscale (Figure 6.2C). The Bland-Altman statistics are showed in Table 6.7**.**

LEFS. The SEM was 4.55 points, which led to a minimal detectable change (MDC_{95}) of 12.62 (Table 6.6). The Bland-Altman plot showed a mean difference between the two applications of the Belgian-Dutch LEFS of 1.13 points (95% CI -2.13 – 4.40) (Figure 6.2G) (Table 6.7).

Table 6.6. Measurement error of Belgian-Dutch DFS-SF and LEFS questionnaires

DFS-SF	ICC	SD	SEM	MDC_{95}
Leisure	0.65	4.79	2.83	7.84
Physical Health	0.62	21.02	12.96	35.92
Dependence/daily life	0.84	17.61	7.04	19.51
Negative emotions	0.62	20.47	12.62	34.98
Worried about ulcers/feet	0.58	21.54	13.96	38.70
Bothered by ulcer care	0.36	18.15	14.52	40.25
LEFS	0.85	11.75	4.55	12.61

DFS-SF: Diabetic Foot Ulcer Scale Short Form; LEFS: Lower Extremity Functional Scale; ICC: Intraclass Correlation Coefficient; SD, Standard Deviation; MDC_{95}: Minimal Detectable Change at the 95% confidence level; SEM: Standard Error of Measurement.

Table 6.7. Bland-Altman statistics

DFS-SF	Mean difference (bias)	Mean SD	95% CI Mean	Upper LOA	Lower LOA
Leisure	0.29	4.79	-1.04 – 1.62	-9.10	9.68
Physical health	3.75	21.02	-2.10 – 9.60	-37.46	44.96
Dependence/daily life	0.10	17.61	-4.81 – 5.00	-34.43	34.62
Negative emotions	1.923	20.47	-3.77 – 7.62	-38.20	42.04
Worried about ulcers/feet	11.66	21.54	5.66 – 17.66	-30.57	53.86
Bothered by ulcer care	1.68	18.15	-3.37 – 6.74	-33.90	37.26
LEFS	1.13	11.75	-2,14 – 4,40	-21.90	24.17

DFS-SF: Diabetic Foot Ulcer Scale Short Form; LEFS: Lower Extremity Functional Scale; SD: Standard Deviation; CI: confidence interval; LOA: limit of agreement; Upper LOA: Mean + 1.96 SD; Lower LOA: Mean - 1.96 SD.

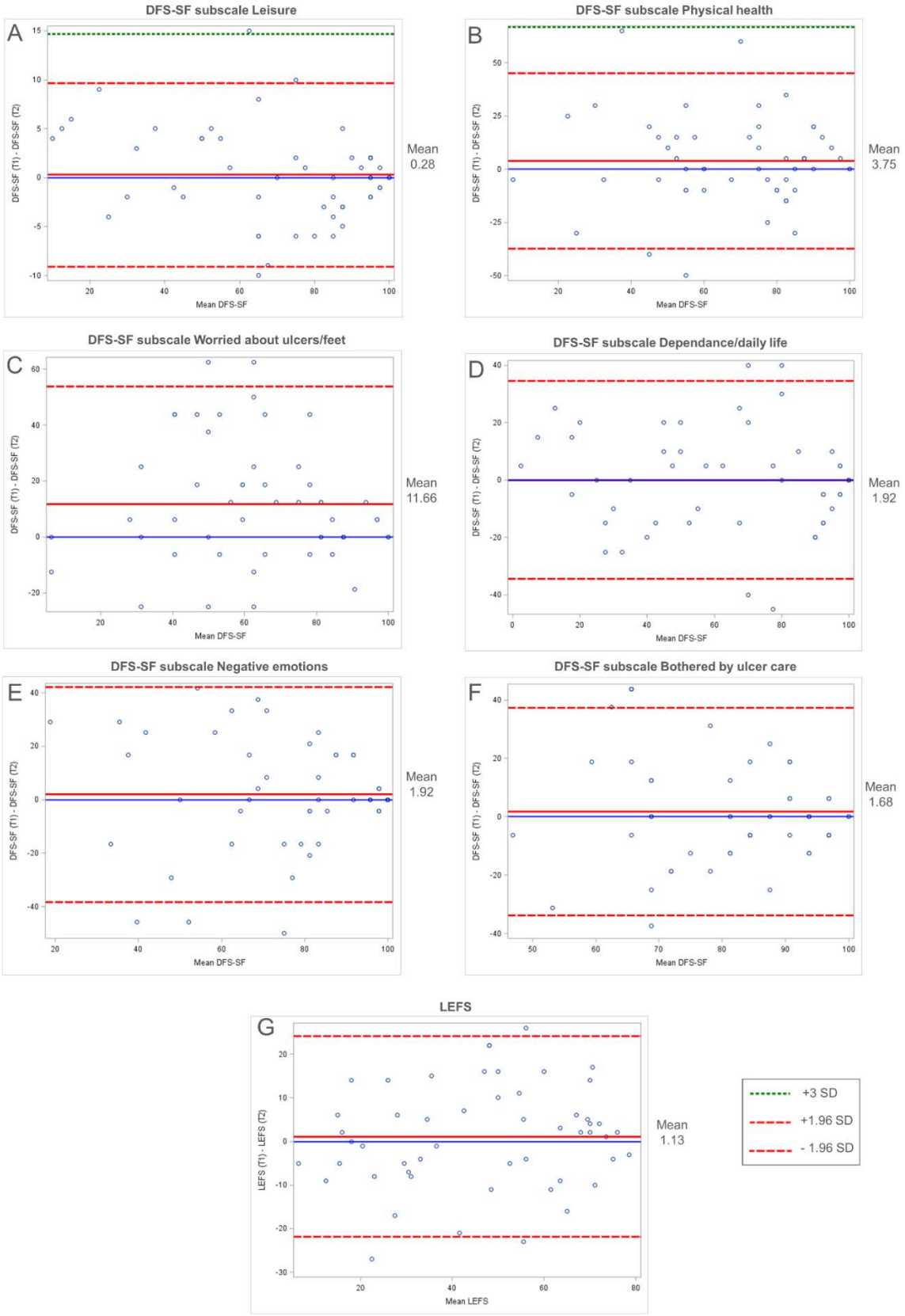

Figure 6.2. Bland-Altman plots for DFS-SF subscales and LEFS. Panels (A-G) plot the difference between two score measurements (Y-axis) against the average of two score measurements (X-axis). Dashed horizontal red lines represent the upper and lower limits of agreement (LOA) at 1.96 or 3 or standard deviations. Solid red line represents the mean difference between the two score measurements (bias).

6.5 Discussion

The aim of this study was to culturally adapt the DFS-SF and LEFS questionnaires for Belgian Dutch-speaking patients with DFU and to assess their reliability by evaluating the following measurement properties: floor and ceiling effects, internal consistency, test-retest reliability and measurement error. In the long term, the broader objective is to provide reliable and valid measurement instruments to capture PROs among Belgian Dutch-speaking patients with DFU that can be used to reflect the patient perspective on his own condition and can serve as QIs quality indicators in quality of care assessment initiatives.

To achieve our aim, we performed a monocentric study including 107 patients with severe DFU. The Belgian-Dutch DFS-SF and LEFS questionnaires found to be internally consistent and reliable to capture PROs among patients with DFU. In the following paragraphs, we will compare our findings to similar studies in the DFU field.

Floor and ceiling effects were calculated to examine the questionnaires' ability to distinguish between patients with the lowest or highest possible score.
Only a limited amount of patients obtained a score 0 (lowest score) for certain subscales of the Belgian-Dutch DFS-SF. However, none of the subscales reached the threshold of 15%, indicating there were no floor effects present in our study. In contrast, ceiling effects were observed in the leisure (16.9%), dependence/daily life (23.8%), negative emotions (18.1%) and bothered by ulcer care (15.2%) subscales. Comparing to what other studies have observed, more pronounced ceiling effects were reported during the validation of the Chinese version of the DFS-SF,[243] with the highest percentage (30.0%) observed in the negative emotions and bothered by ulcer care subscales. The presence of ceiling effects indicates that patients perceived a huge impact on their daily life and wellbeing by the foot ulcer that is higher than can be captured by the questionnaire. Unlike our results, floor effects were reported in the leisure subscale (16.2%) of the Polish DFS-SF version[245] and in the worried about ulcers/feet subscale (19.1%) of the Greek version.[244] These contrasting results may be related to the differences in population characteristics or cultural factors between studies.
No floor or ceiling effects were observed for the Belgian-Dutch LEFS. Similarly, no floor or ceiling effects were found neither in the Dutch LEFS for patients with osteoarthritis,[262] nor in the Spanish[260] and Italian[261] LEFS for patients with any lower-extremity musculoskeletal condition.

Internal consistency was intensively investigated in other language versions of DFS-SF[243–249]. Our values of Cronbach's alpha were, according to the COSMIN quality criteria, good (Cronbach's alpha range: 0.70-0.92) and found to be quite similar to the values reported in the development study of DFS-SF[242] and other validation studies[245,247–249,274]. Of the six subscales, the leisure subscale had a Cronbach's alpha value most frequently > 0.90, which may indicate redundancy of items.

The Belgian-Dutch LEFS showed a Cronbach's alpha of 0.95, indicating a good internal consistency. Our result was comparable to that of the original version[259], which showed a Cronbach's alpha of 0.96 for a similar sample of patients (N=107) but with a different patient condition (any lower-extremity musculoskeletal condition). A similar population was studied in the Spanish[260] and Italian[261] versions, which reported a Cronbach's alpha of 0.94 (N=250) and 0.98 (N=132), respectively.

Test-retest reliability of the Belgian-Dutch DFS-SF and LEFS was assessed with a type 2,1 intraclass correlation coefficient. Except the subscale bothered by ulcer care (ICC = 0.36), our values for the different DFS-SF subscales ranged between 0.58 and 0.84, demonstrating moderate to good reproducibility.

Unlike most other available studies,[242,248,249,275] we reported complete information about the selected ICC form, including the 95% confidence interval of the estimates for each subscale. According to the guideline, if the authors provide incomplete or confusing information about their ICC form used for calculations, its correctness becomes questionable, and the ICC value must be interpreted with caution[267]. The only other study that provided complete information about ICC was the Spanish DFS-SF study[247]. In an apparently similar population, they showed higher values, ranging from good to excellent (0.77-0.92). This may be explained by the fact that they applied a shorter time interval (1 week) between the repeated measurements than in our study (3 weeks).

The ICC of the Belgian-Dutch LEFS was 0.85 (95% CI 0.75 - 0.91). The same type of ICC form was calculated for the Dutch[262], Spanish[260] and Italian[261] LEFS. The highest reliability was demonstrated by the Spanish[260] version, with an ICC value of 0.998 (95% CI: 0.996 to 0.999), considered as excellent. However, their results may be attributed to the application of a shorter time interval (5 days).

No information about measurement error was available among the studies evaluating the measurement properties of the DFS-SF questionnaire[243–249]. Measurement error (or Absolute reliability) refers to the variability of the scores from measurement to measurement (within subject/measurement) and revealed some differences masked by the ICC, expressing the test-retest reliability (or Relative reliability). This is why more than one parameters of reliability should be provided[276,277]. We evaluated the measurement error by using SEM, MDC and Bland-Altman techniques.

The SEM and MDC_{95} values observed for the Belgian-Dutch DFS-SF varied depending on the scale. The largest SEM value was 14.52 points and the largest MDC_{95} value was 40.25 points. This indicated important variations around the obtained scores, and suggested that changes in score (improvement on the scale) must have to be even greater to indicate true changes in the further steps of validation of the Belgian-Dutch DFS-SF. In addition, the Bland-Altman plots disclosed notable differences between two applications (distance of the mean difference from zero) for most of the Belgian-Dutch DFS-SF subscales, with the highest difference observed for the worried about ulcers/feet subscale (11.66 points).

This observed lack of agreement between two measurements from the same participant (within-subject variation) might be attributed to factors such as the emotional status of the patient at the moment of the surveys or the conditions the PROMs questionnaires were administered.
In contrast, measurement error was assessed in various studies considering LEFS. SEM and MDC (90% and/or 95% CI) were calculated by all of them[259–262], while Bland-Altman plot was only produced by the Dutch study[262]. Our values of SEM and MDC_{95} were similar to those reported in the Dutch LEFS version for patients with osteoarthritis, which showed a SEM and MDC_{95} of 4.4 and 12 points, respectively. Interestingly, the mean difference observed between two applications of the Belgian-Dutch LEFS (1.13 points) was smaller than the mean difference displayed for the Dutch LEFS (1.87 points). Unlike our study, the Spanish[260], Italian[261] and original[259] versions studied patients with lower-extremity musculoskeletal condition. The Spanish version showed lower values of SEM and MDC than the values observed in our study and in the original and Italian versions. The disparities observed in measurement error across the various versions of LEFS might be explained by the characteristics of the different study groups, which may influence variations around scores.

This preliminary study contributed to improve future investigations in the evaluation of PROMs instruments for their use in DFCs. We made PROMs understandable and relevant to Belgian Dutch-speaking patients with DFU. We estimated the impact of variations in scores that may be observed in the subsequent validation steps of the Belgian-Dutch DSF-SF and LEFS questionnaires. Our study met the standards about design requirements for studies that evaluates the measurement properties of existing PROMs, including patient stability, appropriate time interval and use of recommended statistical methods. Our main strength was that we clearly described the models or formula for each reliability parameters and provided key information that is often missing in similar studies from literature.

There are some limitations in this study. First, the study population was recruited in one single centre. The selected centre is highly specialized in diabetic foot care and treats a lot of patients. The results obtained in patients followed in such a specialized centre might not be transferrable to other patients. Second, we used a complete case analysis to address missing data, which may have introduced bias. Other techniques like replacing missing values for a variable with its overall estimated mean or with predicted score from a regression equation could strengthen our results. Third, the procedure for administering the questionnaires may represent a source of variations in score measurements. In further steps, the standardization of the procedure may improve the accuracy of measurements, resulting in smaller errors. This could be done by training the interviewers or improving the conditions of administration of PROMs, for instance.

In conclusion, the Belgian-Dutch DSF-SF and LEFS questionnaires demonstrated internal consistency and test-reliability test that positively met the predefined quality criteria and were similar to the findings reported in studies of other language versions, although a certain degree of measurement error was observed. Further steps of the research should concentrate on examining the construct validity, criterion validity, and responsiveness of both questionnaires.

Construct validity reflects the extent to which a particular measure consistently relates to other measures with theoretically derived hypotheses for the constructs that are being measured[231].
Criterion validity refers to the extent to which scores on a particular instrument relate to a gold standard. Finally, responsiveness is defined as the ability of a questionnaire to detect clinically important changes over time, even if these changes are small[278].

Chapter 7

GENERAL DISCUSSION

7.1 A mixed-method approach for improving quality monitoring

The substantial physical, psychosocial and economic impact of DFU has prompted all stakeholders engaged in DFU care to seek efficient systems for monitoring and evaluating the quality of delivered care. However, achieving quality improvement in DFU care is not easy. The field is relatively new and encompasses several layers of complexity. The multifactorial pathophysiology of DFUs makes their understanding and management complex, with various healthcare disciplines interacting with each other, as well as with individuals with DFUs and their relatives, leading to a number of different aspects that can be monitored to improve care within diabetic foot services. Twenty-years ago, quality improvement initiatives in diabetic foot services were established in different countries. Although these projects have great merits, some aspects need to be improved to facilitate the achievement of quality improvement. A certain level of methodological rigor is required to develop QIs that will provide valid and reliable information to HCP for implementing changes and ultimately provide better patient care. QIs should be based on EBM, which means integrating individual clinical expertise with the best available evidence and patient values. The strength of evidence for an indicator will determine its scientific soundness or the likelihood that improvement in the indicator will produce consistent and credible improvements in the quality of care. Nevertheless, before an evidence-based intervention may be turned into a QI, several testing steps will be required. Person-centered care may be promoted within quality initiatives with the integration of patient-reported outcomes. Before testing the implementation of patient-reported data monitoring, the patient-reported measures themselves should be evaluated. Moreover, when comparing the performance between different diabetic foot services, a risk-adjustment strategy must be defined.

Interestingly, the number of publications on diabetic foot has increased exponentially since the exisiting QIs were developed. This suggests that there may be further opportunities for evidence-basedinterventions to improve the quality of care. Additionally, a formalized approach for developing QIs within diabetic foot service audits has been lacking. Therefore, we provided a standardized approach for developing QIs based on literature search and stakeholder consensus. First, in chapter 3, we outlined steps for a methodical and transparent search for evidence-based interventions on which process or structure indicators can be based. We reported our search strategy and eligible criteria to identify primary clinical studies reporting interventions related to organization of care (structure) or delivery of care (process). The level of evidence supporting each candidate QI is transparent when the strength of that evidence is described before the QIs are selected. To describe the evidence provided by a large amount of identified eligible studies, we developed an easy-to-use scoring system to communicate the certainty of evidence supporting the association between an identified intervention and an outcome. Second, we defined the candidate QIs using the standard approach, which consists in stating the indicator as a proportion; that is, define a numerator and a denominator.

In order to provide a clear and detailed numerator and denominator for each candidate indicator, we generated evidence-based statements based on the PICO (population, intervention, control and outcome) criteria, which framed the association between an identified intervention and an outcome. This practice contributed to maintain the definitions for QIs within the same technical specifications for both the numerator and denominator, while ensuring alignment with evolving evidence in DFU care.
Third, in chapter 4, we asked a multidisciplinary group of stakeholders active in DFU care to assess the relevance and feasibility of candidate structure and process QIs formulated in chapter 3, using a RAND/UCLA consensus method. The technique has previously been used to develop QIs for mental health,[200] hip and knee arthroplasty rehabilitation[197] and treatment of lung cancer[199], and provides a quantitative measure of collective judgement. This combines a review of the literature with ratings by an expert panel and, where there are gaps in the literature, on the panel's own experience. In accordance with the RAND/UCLA consensus methodology, a summary of the evidence in table format was provided to each stakeholder in order to assist the comprehension of the collected evidence behind the proposed QIs. Literature may be limited by the fact that supporting high-quality evidence was not always available (or feasible) for some QIs, although the related process or structure of care may already be part of the clinical practice. The reverse situation may also exist where high-quality evidence is present, but due to other reasons such as high costs, the intervention will not be implemented in standard clinical practice. Both situations could receive attention during the evaluation by a stakeholder panel.

In our approach, the use of scientific evidence complemented by a formal consensus increases the validity of QIs, given that they have undergone an objective evaluation by a representative panel of DFU stakeholders, who have judged them logical and clinically appropriate (face validity). Furthermore, the use of evidence-based interventions reported by clinical studies, rather than guideline recommendations, as primary sources, allowed DFU stakeholders to reflect on the feasibility of an indicator, irrespective of whether the intervention has been recommended. It is generally known that assessing feasibility, i.e. the availability of data for establishing the measure during QI development, is worthwhile, as it will make the collection of data and the implementation of care improvement easier in a timely fashion.[122]

However, we were not able to involve individuals who have lived experience of DFU in our panel and who might have brought different perspectives. In the future, this may be overcome by the involvement of patient experts. Patient experts are a group of volunteers that are specifically trained to have a good knowledge of the care system and of their (or their relatives) disease. They may be involved by using focus groups, self-administered questionnaires, or individual interviews.

Taken together, chapters 3 and 4 provided the structured steps for identifying QIs in a more rigorous and transparent manner. From a broader perspective, our standardized approach focused on developing structure and process QIs that aimed to be used in an audit-feedback system. In the literature, Stegbauer *et al.*, who developed QIs for a nationwide QA procedure in mental healthcare, predominantly identified indicators related to process.[200]

Conversely, Neilson *et al.* focused on the identification of outcome indicators in the context of T2D value-based contracts between payers entities and pharmaceutical manufacturers.[279]
Depending on the summative or formative use of QIs and the quality information users, the focus on QI type may be different. For example, most audit-feedback systems, in practice, concentrate on processes of care and/or associated outcomes, emphasizing effectiveness and patient safety.[280] External assessment strategies like accreditation or certification aim to improve the same quality dimensions in addition to person-centeredness, but with a greater attention to indicators of structure and process rather than outcome.[281] Public reporting may include indicators of patient satisfaction and patient experiences to assess person-centeredness as well as QIs related to structure, process and outcome.[282] Because P4P programmes more often reward improvements in health outcomes and patient safety, they may rely more on outcome indicators.[283] Finally, indicators related to structure of care may be more appropriate for strategies that regulated HCP, such as professional licensing or accreditation for education institutions.[284]

In view of promoting person-centered care, quality monitoring initiatives may incorporate patient-reported outcomes. However, the patient-reported measures themselves need to be assessed before testing the implementation of patient-reported data monitoring. Therefore, in chapter 6, we conducted a monocentric observational cohort study to assess the reliability of PROMs, which can be used to gather information about HRQoL of Belgian Dutch-speaking individuals with DFU using consensus-based standards (COSMIN). We showed that the reliability of the Belgian-Dutch version of DFS-SF and LEFS was comparable to those observed in similar studies of other language versions. Moreover, our study conducted a more comprehensive evaluation of the reliability, which resulted in providing key information that is often missing in such studies. Currently, the literature lacks clear evidence about the impact of PROMs, making definitive recommendations premature. A previous systematic review that examined the impact of implementing PROMs into routine clinical practice for non-malignant pain concluded that the poor quality, lack of generalizability and heterogeneity of the included studies hinder a comprehensive understanding of how PROMs may impact clinical treatment.[285] In an oncologic setting, a systematic review of the impact of routine collection of PROs showed conflicting results.[286] There is strong evidence that well-implemented PROs improved communication between patient and HCP, and patient satisfaction, but weak to no evidence for the impact on changes in patient management and health outcomes, patient behavior or quality improvement effectiveness. In addition, some clinicians display skepticism about the meaningfulness of PROMs data, with questions about the validity of the measures employed or concerns about their application.[287] Nevertheless, there are still reasons to belief that the collection of PROs, through the use of reliable and valid self-administered questionnaires (PROMs), may be valuable. First, the use of PROMs can be seen as a tool to strengthen patient empowerment because their completion prompts patients to reflect on their health and allows them to raise issues with clinicians. It has been found that the act of PRO information retrieval can change how patients think about their condition.[288] Second, PRO data offer tremendous opportunities for HCP and health authorities. The report issued by Devlin *et al*. on the implementation of a PROMs programme in the NHS England system, demonstrated the capacity of PROMs to inform decision-making at all levels within the healthcare system.[228]

In order to achieve the potential of PROMs, future research is needed to provide better evidence on the impact of implementing PROs in clinical practice, alongside to an accurate validation of questionnaires.

Undoubtedly, when undertaking quality measurement or making use of quality data, in particular with regard to outcome indicators, a risk-adjustment is essential for fair benchmarking.[132] Therefore, in chapter 5, we developed multivariable models that can be used for risk-adjustment within quality of care initiatives. We adopted a strategy that relied on a large database prospectively collected during the national quality initiative IQED-Foot combined with accurate methods to limit the impact of commonly encountered bias in regression model building. As a result, we provided a detailed methodology to internally validate multivariable risk-adjustment models and perform additional validation using data from a later period (temporal validation), which is already considered as a valuable intermediate approach between internal and external validation.[218] In addition to being used for providing risk-adjusted feedback on DFU healing as an outcome to DFCs, which are subsequently more likely to identify and address clinical care issues that fall under the influence of healthcare intervention, our approach has further applications. First, since we relied on a local database to identify which variables could predict our outcome-of-interest, our bottom-up approach may be used to apply precision medicine.[289] In this context, predictors may be selected based on their importance in the envisioned application setting. For example, geographic factors may be important in a prognostic model developed in a setting where access to specialized centres is an issue. Second, our risk-adjustment strategy may be used in the framework of value-based healthcare programmes, where risk-adjusted outcomes serve to achieve high value for patients and make care more efficient.[106]

In summary, we propose to follow structured steps, which makes the QI development process more rigorous and transparent. In addition, we propose to broaden the scope of quality monitoring by considering the use of PROMs to gain information on HRQoL patient. Finally, we provide a methodology to define risk-adjustment strategy that contributes to make fair comparisons within quality improvement system. While our mixed-method approach lays the groundwork for optimizing quality monitoring of DFU care in specialized diabetic foot services and others areas, some limitations in the scope should be recognized as well. Our research does not address the broader scope of foot care in people with T2DM. In addition, it does not include the subsequent steps required before implementing PROMs in clinical practice or making the identified QIs ready to use. Finally, it mainly searched for interventions supporting QIs that are related to effectiveness of care, missing to cover other quality dimensions, such as efficiency, accessibility, timeliness and equity. Nevertheless, as previously pointed out, this research aimed to improve quality monitoring and QIs in the context of a national quality improvement initiative implemented for Belgian hospitals treating DFU. The primary focus on effectiveness may serve as a catalyst for unlocking the full potential of quality assessment, with the goal of gradually evolving to a more comprehensive delivery of high quality of care.

7.2 Identification of new indicator topics

The development of a mixed-method approach provided for the improvement of quality monitoring in DFCs as disseminated through the different chapters of this PhD dissertation, contributed to reinforce some topics for QIs but also bring new ones. In what follows, these insights will be discussed in the perspective of the diabetic foot world, according to Donabedian's triad related to the three different aspects of healthcare: structure, process and outcome of care.

Structure indicators

During our stakeholder panel, four evidence-based interventions related to the structure of care were judged appropriate for being used as QI. Among them, topics commonly reported in the literature such as the establishment of a multidisciplinary team approach or the integration of podiatric care were identified. Also less frequently described indicator topics, such as the availability of a skilled wound care specialty and the implementation of protocolized care, came out of our work. Both topics have been missing in the Belgian,[143] German[63] and UK[146] foot services audits so far. Currently, the Belgian diabetic foot convention encompasses criteria on structure of care, which cover mandatory staffing of various specialized disciplines and additional organizational requirements such as consultation hours availability and dedicated consultation rooms.[151] Similarly, German DFCs are required to document interdisciplinary collaborations, provide facility's spatial condition and justify any deviation from the procedure in order to get certification.[290] In the UK, the involvement of a member from an expert Multidisciplinary Foot Care Team is registered as well.[150] Regardless of the country, the implementation of our findings will inevitably raise a number of practical questions related to financial or legal aspects. In Belgium, for instance, HCP are strictly regulated with recognition criteria providing the license to practice.[291] The integration of a wound care specialist would therefore require that skills are defined and recognized for potential future implementation in the diabetic foot convention. An official recognition of the specialty may encourage HCP to extend their knowledge of new therapies like bioengineered skin substitutes or isolated cellular therapy. Nevertheless, technical issues related to the storage of such products that requires specific conditions to maintain cell viability may represent a barrier to implementation. Furthermore, questions related to the coordinating role associated with this specialty may emerge.

The implementation of a P4P strategy emerged from our scoping review and was proposed to the stakeholder panel, but was finally not selected. In Belgium, recognized DFCs receive a standard fee per patient visit, but there is no incentive payment for reaching targets.[151] In Italy, on the other hand, a regional governance system including a P4P model has been implemented in DFCs.[154,292] The model shares similarities with the Belgian model in the use of a performance evaluation system based on benchmarking and the establishment of a stable community of professionals to discuss data and practices. Both systems collect outcome data on major amputations, for instance. Nevertheless, unlike in Belgium, economic incentives like Chief Executive Officer rewards are applied and the public disclosure of the data does lead to reputational competition.[154]

The public disclosure of the performance information is facilitated by the use of a five-coloured assessment system based on the benchmark results (dartboard diagram). Performance on major amputations is reported by assigning five colour bands considering the overall average and the distribution of hospital results. In literature, conflicting evidence about the impact of P4P programmes has been reported. In primary and acute hospital care across various fields, P4P programme implementation resulted in a broad spectrum of possible effects for specific targets, from absent or negligible to strongly beneficial.[293] In DFCs, P4P initiative is particularly challenging due to the high level of complexity with different patient characteristics that need to be taken into account. In addition, the P4P initiative always carries the risk that overly complex patients will be refused (negative selection).

Similarly to what has been observed in the literature and regardless the medical field, only a small number of identified evidence-based interventionsin this PhD research addressed structure of care. This may be attributed to the difficulty in establishing the association between structure and outcome. Another potential explanation is that this is often a matter of national policy, with all hospitals in a country required to adhere to the same standards (for example, in Belgium the diabetic foot convention specifies opening hours or team composition).[151] Nevertheless, the existing literature suggests that structural aspects, such as nurse staffing availabilities, may be associated with better outcomes.[294,295] In this context, it is important to continue the development of measures of structure that take into account physical environment, working conditions, organizational culture and HCP satisfaction.[296] This would enable, for instance, to draw attention to the lived realities of HCPs and integration of new quality dimensions such as kin-centredness, as initiated by Lachman, Batalden and Vanhaecht.[107]

Process indicators

Thirteen of the seventeen evidence-based interventions identified through our standardized approach were related to process of care. Two of these interventions, which focused on the evaluation of the nutritional status of the patient and the administration of low-density lipoprotein (LDL)-cholesterol-lowering medication, had not been considered so far. Both topics highlighted the need for a more holistic view on the DFU treatment. Consistently, a recent review investigating the relation between malnutrition and DFU severity and outcome indicated that malnutrition is highly prevalent among DFU patients and might have a negative influence on DFU outcomes.[181] The Australian National Diabetes Audit study group published findings showing that dietary supplementation is associated with increased odds of DFU healing at 6 months.[297] In Australia, these topics have been addressed within a national strategy, which aims to improve the prevention, early detection, management and care of all types of diabetes. In the currently ongoing Belgian IQED-Foot data collection, two new items on the evaluation of the nutritional status and the patient anthropometry have been added in the electronic questionnaire.[298] Outside the field of diabetes, indicators related to the nutritional status of the patient have also been used. QIs related to the assessment of obesity using BMI was developed by *Westby et al*. to monitor rehabilitation care for hip and knee arthroplasty.[197] Further, outcomes indicators related to the weight loss and weight change were identified by *Wagner et al.* to measure the quality of home care.[299]

Our approach for indetifying QIs confirmed the appropriateness of a set of evidence-based interventions to be used as QIs, covering local wound care, means of offloading, revascularization procedures, and delivery of preventive measures. These are management principles that take into account the complexity of DFU and its numerous manifestations, and should therefore be used as markers of quality in any diabetic foot service. Some of these interventions are also considered for improving quality of care in other medical fields. For instance, reperfusion therapy (fibrinolytic therapy or percutaneous coronary intervention) has been defined as performance measure for the management of acute myocardial infarction. Similarly, this measure is meant to assist clinicians in assessing the appropriateness of their use of reperfusion therapy and detecting underutilization of reperfusion.[300] In the Belgian as well as in the German diabetic foot audit, data about revascularization (endovascular and bypass surgery) and amputation procedures (minor and major) are recorded.[63] With regard to preventive measures, only in the UK audit, information related to the availability of education programmes for people defined as being at increased risk is collected.[150] Nevertheless, a topic for QI addressing the delivery of patient education also came out of our work.

Although essential interventions for process QIs have been defined, differences in all kinds of processes applied in the DFC setting may persist between countries. This may be related to the reimbursement system, the organization of care or the availability of qualified staff. In the UK, for instance, obtaining data on the use of diabetic footwear is difficult, largely because footwear is often prescribed by orthotic services, which consists of HCP specialized in biomechanical problems and for which no national dataset is available.[301] In Belgium, orthopaedic surgical and vascular surgeon disciplines within DFCs can prescribe footwear for secondary prevention facilitating the collection of data about their provision.[151] During our consensus panel, the use of non-removable knee-high offloading devices was confirmed as an appropriate indicator for assessing quality. Currently, it is considered as a standard of care for offloading, along with non-removable knee-high walking casts. Nevertheless, issues related to staff expertise or equipment availability were raised. Similar issues may explain the infrequent use of any form of casting in Germany.[142] In a non-Western practice, the situation can be entirely different. On the African continent, difficulties related to access to facilities or knowledge of DFU by individual healthcare workers represent a major issue.[135] In this context, the delivery of educational interventions has represented the most powerful tool, with the implementation of educational programmes like “Step by step foot project” or “Train the foot trainer” as examples. Taking into account the local perspectives constitutes a strategy for overcoming barriers and creating changes across DFCs. In this regard, the bottom-up approach that we adopted in Chapter 5 may represent an interesting strategy since it allows to tailor clinical risk assessment and evaluation of care to the local needs.

Outcome indicators

Benchmarking within an audit setting can provide evidence of variation in outcomes between different diabetic foot services, which can be used as the basis of improving quality of care and outcomes. The accuracy and fairness of benchmarking can be improved by risk-adjustment. In our research, a risk-adjustment strategy was defined using the measures of ulcer healing collected within IQED-Foot.
Similarly, the UK audit also developed multivariable risk-adjustment models for DFU healing.[146] In diabetic foot care, there is a consensus on the main outcome measures that should be collected, and therefore be subject to risk-adjustment. These include ulcer healing, major amputation and death. Ulcer healing is a desirable outcome as normal function is restored and skin integrity is regained, thus reducing the risk for infection. Nevertheless, despite the provision of optimal care the wound may fail to heal and even deteriorate. In such a case, wound healing may no longer be a primary objective, leading to two management options; limb salvage therapy with a non-healing wound, on condition that this is in the best interests of the patient, or major amputation.[302] On the one hand, major amputation is generally regarded as an outcome that should be avoided at all cost. It reduces patient mobility, is associated with high medical costs[82] and generates fear in people with DFU.[69] On the other hand, major amputation may represent the best outcome, and may be preferred by the patient over living with a chronic ulceration that requires daily care.[303] The measure has been shown easy to document in hospitals with a certain degree of reliability.[304] In Belgium, for example, major amputation can be measured using administrative hospital data.[61] However, major amputation is a relatively uncommon outcome, with about 3% of severe ulcers resolved by major amputation within 6 months in Belgian DFCs.[143] In addition, differences in the definition of major amputation may make comparisons difficult. Another relevant outcome indicator is mortality due to the high risk associated with DFU.[21]

Besides healing, major amputation and death, two additional outcomes may give a more complete view of the effectiveness of management and prevention of DFUs. The first is recurrence. It enables to think of patients who have achieved wound closure as being in remission rather than being healed. The concept of remission may provide a better framework for allocating resources, organizing care, and communicating information about risk.[152] The other is the recently proposed ulcer-free time.[53] This outcome is interesting because it allows to consider the presence of multiple ulcers and the consultation of several centres. From a patient perspective, ulcer-free time can be more relevant as it represents the estimated time it is likely to take until all the ulcers are healed (being ‘ulcer-free’). A recent study indicated that ulcer-free survival days are related to variables that explain poor healing outcomes and, presumably, recurrence.[305] Nevertheless, for both measures, the reliability of data collection may be compromised due to the difficulty of follow-up across different HCP and centres.

Currently, the Belgian, German and UK foot audits collect data on ulcer healing, mortality rate, and amputations (minor and major). Belgium and Germany collect the outcome data at 6 months. In the same time interval, Belgium collects the recurrence rate (relapse or new ulcers). The date of death is since recently retrieved from the national registry, which enhances the reliability of the data and enables collection beyond 6 months.

In the UK, ulcer healing is registered at 12 weeks, while mortality and major amputation within 6 months. Recently, they added the state of being 'alive and major amputation-free at 1 year' for assessing the long-term response to an intervention. Depending on the outcome measure, it seems logical to apply the same length of follow-up across the different national audits to make accurate comparisons or to perform time-to-event analysis.

While a 6-month follow-up may be ideal for assessing DFU healing, it may be less appropriate for assessing ulcer-free status or survival because it is too short to observe sufficient events of ulcer recurrence, new ulceration, limb salvage or death. In Belgium, the linkage to the national registry enables survival data to be updated on daily basis.

When comparing QIs, the alignment of definitions facilitates comparison across diabetic foot services. The information about the factors influencing DFU outcomes should be the same as well. In our risk-adjustment approach, five essential outcome determinants emerged, including referral time, history of minor amputation, ulcer location, surface area and ischemia. Whereas ulcer characteristics can be based on existing classification systems, there is currently no consensus on the definition of what constitutes a delay or the timeframe within which specialist care and treatment should be provided.[49] In the UK audit, the referral delay is studied by collecting time from first presentation with the ulcer to any healthcare professional and its first expert assessment by a member of a specialist foot care team in either the community or the hospital. In Belgium, the presentation delay is defined as "the number of weeks the foot problem existed before the first consultation in the DFC". However, these discrepancies should not prevent referral time from being investigated since it represents an important element of quality of care in achieving timely care. In other medical conditions such as acute stroke, for instance, the time of presentation is crucial to maximize the benefits of stroke intervention. Guidelines recommend treatment within 3 hours after the onset of stroke symptoms.[306] In DFU care, notwithstanding the lack of consensus on the definition of referral interval time, notable efforts have been made to minimize delayed referral, and consequently reduce adverse outcomes. For instance, a fast-track pathway (FTP) for DFU has been developed under the initiative of the International Diabetic Foot Care Group (IDFCG) and D-Foot International.[50] The project has been designed for not-expert HCP and aims to detect ulcer severity, the specific management and timing of referral to DFC. The pathway can be adapted to the local healthcare systems, respecting the main principles of the programme and has already been tailored for use in Spain, Germany, England, Italy and Flanders (Belgium). A recent Italian study which investigated the effectiveness of the pathway observed lower cases of late referral in comparison to early referral (20.5% vs. 79.5%) after the implementation.[307]

In this PhD dissertation, we addressed the topic of PROs, in the context of assessing PROMs for a potential future integration in quality improvement initiatives occurring in DFCs. We assessed the DFS-SF questionnaire, which was designed to measure the impact of DFU on HRQoL issues most important to patients, including domains such as physical health, dependence/daily life or negative emotions. [242] In addition, we investigated the LEFS questionnaire that demonstrated differentiating pain and physical functioning in wide range of lower extremity musculoskeletal conditions.[258,259]

Both instruments have met predefined quality criteria of reliability and may offer great insight into specific issues impairing the health status of patient with DFU. Among the aspects evaluated by DFS-SF, a particular attention should be paid to depression. In a study among people with their first DFU, one third of the sample population was affected by depression. Compared with no depression, both minor and major depressive disorders were associated with a twofold increased mortality risk at a 5-year follow up.[308] Although evidence on the role of psychological factors such as depression is still scarce, psychosocial screening has been advocated for all people with diabetes,[68,309] and particularly those with diabetic neuropathy because of the clear impact on HRQoL. For this purpose, screening instruments for depression such as the Patient Health Questionnaire-9 (PHQ-9) may be used.[310] However, as with all patient self-questionnaires used in a clinical setting, this needs to be tested before implementation. In this respect, the assessment approach for PROMs that we have reported, may contribute to a further use in diabetic foot services.

7.3 Future directions for performing quality improvement in diabetic foot clinics

Our research adressed some aspects of care that require deeper development.

An essential finding related to the structure of care that emerged from our approach was the significant influence of a timely referral on DFU healing. There is a long-standing concern about the late presentation and delayed management of patients with DFU leading to worse outcomes.[221,222] Time delays may exist in all aspects of the management pathway, and can be considerable in length in some cases.[49] In this context, efforts should be made for acquiring accurate data for investigating referral time in the context of an audit. For example, efforts should be made in strengthening the collaboration with the first line using fast referral programmes such as FTP at a national level.

Regarding the outcome measures, while we only considered ulcer healing in our risk-adjustment approach, it may be interesting to consider new outcome measures such as ulcer-free time. Greater attention should be given to timeliness. Currently, the occurrence of a single ulcer is the starting time point used. However, new ulcers may develop in the meantime, resulting in different timelines in the same person and making the selection of the most appropriate timeline difficult. The implementation of new outcome measures could be facilitated by the use of linkage with administrative data.

Furthermore, our research attempted to fill the significant gap in the field of patient HRQoL information. The collection of PROs has been reported to be valuable for multiple healthcare stakeholders. Future studies should concentrate on assessing additional quality aspects of DFS-SF and LEFS defined by COSMIN,[230] including the construct validity, criterion validity, and responsiveness. Moreover, the feasibility of implementing PROMs in clinical practice and in QA initiative should be investigated. A consensus-based guideline on the methods for selecting outcome measurement instruments proposed various feasibility aspects that should be taken into consideration, among them: patient's comprehensibility, interpretability, length of the outcome measurement instrument and completion time. Along with the use of PROMs, psychological intervention programs should be implemented to increase the patient's psychological flexibility in the presence of pain and to accomplish improvement to functioning, which ultimately may improve patient's quality of life.

Since 2005, IQED-Foot has documented various process and outcomes of care, with a consistent participation rate from the involved centres. This thesis reinforced the QIs currently used in IQED-Foot and provided new insights regarding the aspects of care that may be explored for improving quality of care within DFCs. The new topics issued from our research deserve implementation, but testing steps will need to be performed before. The practical feasibility of each QI should be investigated to identify characteristics that may need to be more detailed, or for which the data to obtain may not be available. Such pilot testing can generally be performed on a small sample of DFCs and/or patients.

In addition, the measurement properties of QIs could be evaluated. Finally, an impact analysis may be conducted to evaluate whether implementation of QIs changes structure or processes of care and improves patient outcomes and/or reduces costs on the long term.

In accordance with their responsibilities, the group of experts of IQED-Foot will have to be engaged in the decision of keeping a currently used QIs, updating it or testing a new measure based on our findings. Resource requirements for the implementation of new QIs should be evaluated. In this context, a discussion with the Ministry of Health, NIHDI and the Belgian Health Data Agency will be needed to ensure that data can be more easily extracted from electronic medical records to reduce the workload of data input. Moreover, the IQED-Foot data should be easily linkable to other databases containing information on treatments, comorbidities, hospitalizations, mortality, social dependency, and cost to maximize the reuse of already collected data. Ideally, this would be embedded in a national data strategy. Finally, Belgian data should be compatible with other existing international data sources allowing regular comparisons in order to enhance global improvement of diabetic foot care. An example of implementation of a large international benchmarking in the field of diabetes is the SWEET registry in which each member electronically transfer de-identified clinic data to a single database, encouraging members to provide increasingly accurate and complete data.[311] Benchmarking and data validation reports are then disseminated to members to identify weaknesses and support the implementation of changes.

Currently, several quality improvement strategies are conjointly being organized so that DFCs use IQED-Foot data in a meaningful manner. PDSA cycles, which guides HCP through a prescribed four-stage learning approach to introduce, evaluate and progressively adapt changes aimed at improvement,[312] are encouraged based on the knowledge gained from the individual feedback reports that the DFCs received after each audit. In the next audit cycle, implemented actions are evaluated and can be adjusted based on the new report. In addition, DFCs have the opportunity to discuss results at national meetings, with practical workshops on topics that need improvement or show high variation among the different DFCs. This initiative can be supplemented by the participation to a peer visit where members of one DFC visit another DFC and exchange experiences and best practices. It would be beneficial if support to the HCP for such peer visits would be foreseen through the convention with the NIHDI. Moreover, quality trainings should be proposed to HCP within DFCs. This training should teach basic principles about the existing quality improvement strategies, the collection of QIs, team collaboration and the person-centered approach. They may empower HCP from diabetic foot services to provide high-quality of care and positively impact outcomes.

Chapter 8

SCIENTIFIC ACKNOWLEDGEMENTS, PERSONAL CONTRIBUTION AND CONFLICT OF INTEREST

Chapter 3: Evidence-based interventions for identifying candidate quality indicators to assess quality of care in diabetic foot clinics: a scoping review

Personal contribution

Flora Mbela Lusendi performed the search strategy for the scoping review, which was validated by Kris Doggen. Flora Mbela Lusendi conducted the selection of articles with the help of Kris Doggen. Flora Mbela Lusendi extracted data with the help of An-Sofie Vanherwegen, Frank Nobels and Giovanni Matricali. Flora Mbela Lusendi designed and implemented the scoring system with the help of An-Sofie Vanherwegen, Kris Doggen, Frank Nobels and Giovanni Matricali. Flora Mbela Lusendi contributed to the drafting of the manuscript. An-Sofie Vanherwegen, Kris Doggen, Frank Nobels and Giovanni Matricali reviewed the manuscript.

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Conflict of interest statements

The authors have declared that no conflict of interest exists.

Chapter 4: A multidisciplinary Delphi consensus to define evidence-based quality indicators for diabetic foot ulcer care

Personal contribution

Flora Mbela Lusendi handled the consensus-building exercise with the support of An-Sofie Vanherwegen, Frank Nobels and Giovanni Matricali. Flora Mbela Lusendi contributed to the drafting of the manuscript. An-Sofie Vanherwegen, Kris Doggen , Frank Nobels and Giovanni Matricali reviewed the manuscript.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors have declared that no conflict of interest exists.

Chapter 5: Bottom-up approach to build a 'precision' risk factor classification for diabetic foot ulcer healing. Proof-of-concept

Personal contribution

Flora Mbela Lusendi and Kris Doggen contributed to the study concept and design, the conducting of statistical analyses and the interpretation of results. Flora Mbela Lusendi contributed to the drafting of the manuscript. Giovanni Matricali,An-Sofie Vanherwegen, Kris Doggen and Frank Nobels revised the manuscript critically for important intellectual content. An-Sofie Vanherwegen assisted in the follow-up of the revision procedure at the Diabetes Research and Clinical Practice journal.

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The authors have declared that no conflict of interest exists.

Chapter 6: Assessing patient-reported outcome measurements, potential source of indicators.

Wahid Rezaie and Frank Nobels designed the study. Annick Staelens collected PROMs and provided the anonymized clinical database. Flora Mbela Lusendi performed preliminary analyses. An-Sofie Vanherwegen analysed the data and interpreted results. Flora Mbela Lusendi drafted the chapter. Giovanni Matricali, An-Sofie Vanherwegen , and Frank Nobels revised the chapter.

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Chapter 9

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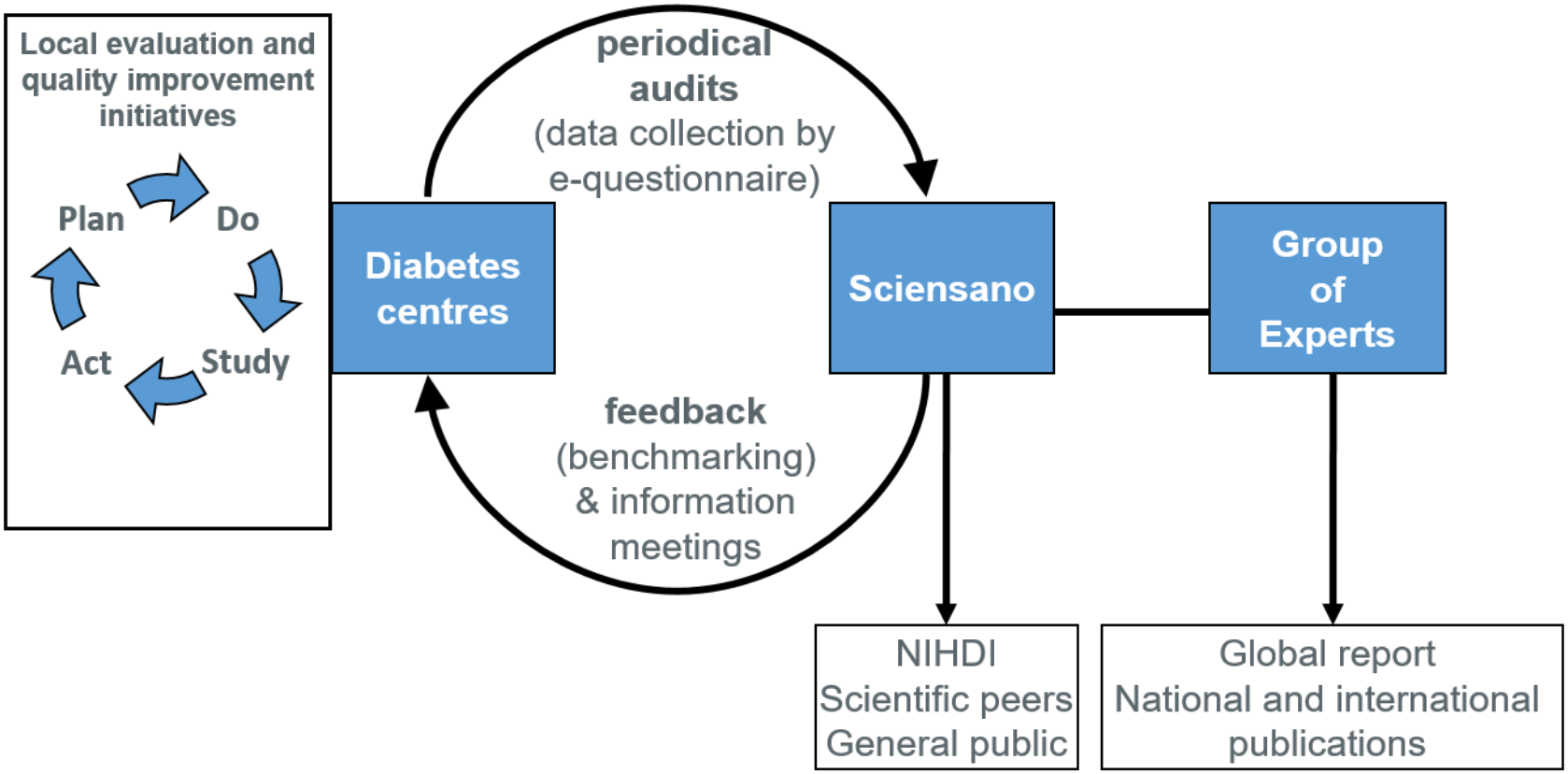
APPENDIX

Appendix to chapter 1



Appendix 1.1. The Belgian audit-feedback system IQED-Foot. The system consists of audit-feedback cycles and anonymous benchmarking, involving different stakeholders. PDSA cycles are encouraged based on the knowledge gained from the individual feedback reports that diabetes centres (DFCs) received after each audit. A global report based on the aggregated national results is available for health authorities (NIDHI) and the general public.

Appendix 1.2. Overview of the quality indicator dataset collected for patients with DFU during the last completed IQED-Foot data collection (2022-2023)

Indicator	Numerator	Denominator
STRUCTURE INDICATORS		
REFERRAL		
Proportion of patients with a DFU that came on their own initiative.	Patients with a DFU that were not referred to the DFC by a healthcare professional.	Patients with a DFU and known referral pattern.
Proportion of patients with a DFU and a history of foot problems that came on their own initiative.	Patients with a DFU and a history of a previous DFU or a previous Charcot foot that were not referred to the DFC by a healthcare professional.	Patients with a DFU and a history of a previous DFU or a previous Charcot foot and known referral pattern.
Proportion of patients with a DFU that where referred to the DFC by a healthcare professional.	Patients with a DFU that were referred to the DFC by a healthcare professional.	Patients with a DFU and known referral pattern.
Proportion of patients with a DFU and a history of foot problems that where referred to the DFC by a healthcare professional.	Patients with a DFU and a history of a previous DFU or a previous Charcot foot that were referred to the DFC by a healthcare professional.	Patients with a DFU and a history of a previous DFU or a previous Charcot foot and known referral pattern.
Median presentation delay	Median presentation delay	Patients with a DFU and known presentation delay, calculated based on a known date of first contact with a member of the diabetic foot clinic for the index foot problem and a known approximate date on which the index foot problem started.
Proportion of patients with a DFU and a presentation delay of more than 4 weeks.	Patients with DFU that have a presentation delay of more than 4 weeks.	Patients with a DFU and known presentation delay, calculated based on date of first contact with a member of the diabetic foot clinic for the index foot problem and approximate date on which the index foot problem started.

Appendix 1.2. Continued

PROCESS INDICATORS		
WOUND CARE		
Proportion of patients with a DFU that received out-patient sharp debridement.	Patients with a DFU that received out-patient sharp debridement.	Patients with a DFU.
Proportion of patients with a DFU that received out-patient sharp debridement performed by a nurse.	Patients with a DFU that received out-patient sharp debridement performed by a nurse.	Patients with a DFU that received out-patient sharp debridement.
Proportion of patients with a DFU that received out-patient sharp debridement performed by a podiatrist.	Patients with a DFU that received out-patient sharp debridement performed by a podiatrist.	Patients with a DFU that received out-patient sharp debridement.
Proportion of patients with a DFU that received out-patient sharp debridement performed by a medical doctor.	Patients with a DFU that received out-patient sharp debridement performed by a medical doctor.	Patients with a DFU that received out-patient sharp debridement.
Proportion of patients with a DFU that received surgical debridement.	Patients with a DFU that received surgical debridement.	Patients with a DFU.
Proportion of patients with a DFU that received any kind of debridement.	Patients with a DFU that received out-patient sharp or surgical debridement.	Patients with a DFU.
Proportion of patients with a DFU and without ischemia that received out-patient sharp debridement.	Patients with a DFU and without ischemia (PEDIS-P = 1) that received out-patient sharp debridement.	Patients with a DFU and without ischemia (PEDIS-P = 1).
Proportion of patients with a DFU and without ischemia that received surgical debridement.	Patients with a DFU and without ischemia (PEDIS-P = 1) that received surgical debridement.	Patients with a DFU and without ischemia (PEDIS-P = 1).
Proportion of patients with a DFU and without ischemia that received any kind of debridement.	Patients with a DFU and without ischemia (PEDIS-P = 1) that received out-patient sharp or surgical debridement.	Patients with a DFU and without ischemia (PEDIS-P = 1).

Appendix 1.2. Continued

WOUND CARE		
Proportion of patients with a DFU and subcritical ischemia that received out-patient sharp debridement.	Patients with a DFU and subcritical ischemia (PEDIS-P = 2) that received out-patient sharp debridement.	Patients with a DFU and subcritical ischemia (PEDIS-P = 2).
Proportion of patients with a DFU and subcritical ischemia that received surgical debridement.	Patients with a DFU and subcritical ischemia (PEDIS-P = 2) that received surgical debridement.	Patients with a DFU and subcritical ischemia (PEDIS-P = 2).
Proportion of patients with a DFU and subcritical ischemia that received any kind of debridement.	Patients with a DFU and subcritical ischemia (PEDIS-P = 2) that received out-patient sharp or surgical debridement.	Patients with a DFU and subcritical ischemia (PEDIS-P = 2).
Proportion of patients with a DFU and critical ischemia that received out-patient sharp debridement.	Patients with a DFU and critical ischemia (PEDIS-P = 3) that received out-patient sharp debridement.	Patients with a DFU and critical ischemia (PEDIS-P = 3).
Proportion of patients with a DFU and critical ischemia that received surgical debridement.	Patients with a DFU and critical ischemia (PEDIS-P = 3) that received surgical debridement.	Patients with a DFU and critical ischemia (PEDIS-P = 3).
Proportion of patients with a DFU and critical ischemia that received any kind of debridement.	Patients with a DFU and critical ischemia (PEDIS-P = 3) that received out-patient sharp or surgical debridement.	Patients with a DFU and critical ischemia (PEDIS-P = 3).
Proportion of patients with a DFU that received out-patient negative pressure therapy.	Patients with a DFU that received out-patient negative pressure therapy.	Patients with a DFU and which are suited for out-patient negative pressure therapy.

Appendix 1.2. Continued

WOUND CARE		
Proportion of patients with a DFU for which a wound tissue sample was sent for microbiological examination.	Patients with a DFU for which a wound tissue sample was sent for microbiological examination.	Patients with a DFU.
Proportion of patients with a DFU and a deep infection for which bone biopsy was sent for microbiological examination.	Patients with a DFU and a deep infection (PEDIS-I = 3) for which bone biopsy was sent for microbiological examination.	Patients with a DFU and a deep infection (PEDIS-I = 3).
OFFLOADING		
Proportion of patients with a DFU where the podiatrist was involved in fitting the offloading device.	Patients with a DFU where the podiatrist was involved in fitting the offloading device.	Patients with a DFU that received any kind of offloading.
Proportion of patients with a DFU that received any kind of offloading.	Patients with a DFU that received any kind of offloading.	Patients with a DFU.
Proportion of patients with a DFU that received knee-high offloading.	Patients with a DFU that received knee-high offloading by total contact cast or (non-)removable knee-high offloading devices.	Patients with a DFU.
Proportion of patients with a DFU that received offloading by total contact cast.	Patients with a DFU that received offloading by total contact cast.	Patients with a DFU.
Proportion of patients with a DFU that received offloading by non-removable knee-high offloading devices.	Patients with a DFU that received offloading by non-removable knee-high offloading devices.	Patients with a DFU.
Proportion of patients with a DFU that received offloading by removable knee-high offloading devices.	Patients with a DFU that received offloading by removable knee-high offloading devices.	Patients with a DFU.

Appendix 1.2. Continued

OFFLOADING		
Proportion of patients with a DFU that received ankle-high offloading.	Patients with a DFU that received ankle-high offloading by using an ankle-high cast or an offloading shoe.	Patients with a DFU.
Proportion of patients with a DFU that received offloading by using an ankle-high cast.	Patients with a DFU that received ankle-high offloading by using an ankle-high cast.	Patients with a DFU.
Proportion of patients with a DFU that received offloading by using an offloading shoe.	Patients with a DFU that received ankle-high offloading by using an offloading shoe.	Patients with a DFU.
Proportion of patients with a DFU that received offloading around the ulcer.	Patients with a DFU that received offloading around the ulcer.	Patients with a DFU.
Proportion of patients with a DFU on the plantar forefoot without PAD that received any kind of offloading.	Patients with a DFU on the plantar forefoot without PAD (PEDIS-P = 1) that received any kind of offloading.	Patients with a DFU on the plantar forefoot without PAD (PEDIS-P = 1).
Proportion of patients with a DFU on the plantar forefoot without PAD that received knee-high offloading.	Patients with a DFU on the plantar forefoot without PAD (PEDIS-P = 1) that received knee-high offloading by total contact cast or (non-)removable knee-high offloading devices.	Patients with a DFU on the plantar forefoot without PAD (PEDIS-P = 1).
Proportion of patients with a DFU on the plantar forefoot without PAD that received offloading by total contact cast.	Patients with a DFU on the plantar forefoot without PAD (PEDIS-P = 1) that received offloading by total contact cast.	Patients with a DFU on the plantar forefoot without PAD (PEDIS-P = 1).

Appendix 1.2. Continued

OFFLOADING		
Proportion of patients with a DFU on the plantar forefoot without PAD that received offloading by non-removable knee-high offloading devices.	Patients with a DFU on the plantar forefoot without PAD (PEDIS-P = 1) that received offloading by non-removable knee-high offloading devices.	Patients with a DFU on the plantar forefoot without PAD (PEDIS-P = 1).
Proportion of patients with a DFU on the plantar forefoot without PAD that received offloading by removable knee-high offloading devices.	Patients with a DFU on the plantar forefoot without PAD (PEDIS-P = 1) that received offloading by removable knee-high offloading devices.	Patients with a DFU on the plantar forefoot without PAD (PEDIS-P = 1).
Proportion of patients with a DFU on the plantar forefoot without PAD that received ankle-high offloading.	Patients with a DFU on the plantar forefoot without PAD (PEDIS-P = 1) that received ankle-high offloading by using an ankle-high cast or an offloading shoe.	Patients with a DFU on the plantar forefoot without PAD (PEDIS-P = 1).
Proportion of patients with a DFU on the plantar forefoot without PAD that received offloading by using an ankle-high cast.	Patients with a DFU on the plantar forefoot without PAD (PEDIS-P = 1) that received ankle-high offloading by using an ankle-high cast.	Patients with a DFU on the plantar forefoot without PAD (PEDIS-P = 1).
Proportion of patients with a DFU on the plantar forefoot without PAD that received offloading by using an offloading shoe.	Patients with a DFU on the plantar forefoot without PAD (PEDIS-P = 1) that received ankle-high offloading by using an offloading shoe.	Patients with a DFU on the plantar forefoot without PAD (PEDIS-P = 1).
Proportion of patients with a DFU on the plantar forefoot without PAD that received offloading around the ulcer.	Patients with a DFU on the plantar forefoot without PAD (PEDIS-P = 1) that received offloading around the ulcer.	Patients with a DFU on the plantar forefoot without PAD (PEDIS-P = 1).

Appendix 1.2. Continued

OFFLOADING		
Proportion of patients with a DFU that are able to stand or walk without help and received any kind of offloading.	Patients with a DFU that are able to stand or walk without help and received any kind of offloading.	Patients with a DFU that are able to stand or walk without help.
VASCULAR EXAMINATIONS		
Proportion of patients with a DFU where a clinical investigation of foot pulses was performed.	Patients with a DFU where a clinical investigation of foot pulses was performed.	Patients with a DFU.
Proportion of patients with a DFU where an arterial Doppler exam was performed.	Patients with a DFU where an arterial Doppler exam was performed.	Patients with a DFU.
Proportion of patients with a DFU where the ankle-brachial index (ABI) was determined.	Patients with a DFU where the ankle-brachial index (ABI) was determined.	Patients with a DFU.
Proportion of patients with a DFU where a toe pressure measurement was performed.	Patients with a DFU where a toe pressure measurement was performed.	Patients with a DFU.
Proportion of patients with a DFU where a $TcpO_2$ measurement was performed.	Patients with a DFU where a $TcpO_2$ measurement was performed.	Patients with a DFU.
Proportion of patients with a DFU where a non-invasive vascular examination was performed.	Patients with a DFU where a non-invasive vascular examination (foot pulses, ABI, toe pressure, TcPO2, arterial Doppler exam) was performed.	Patients with a DFU.
Proportion of patients with a DFU without PAD where a non-invasive vascular examination was performed.	Patients with a DFU and without PAD (PEDIS-P = 1) where a non-invasive vascular examination (foot pulses, ABI, toe pressure, TcPO2, arterial Doppler exam) was performed.	Patients with a DFU and without PAD (PEDIS-P = 1).

Appendix 1.2. Continued

VASCULAR EXAMINATIONS		
Proportion of patients with a DFU and subcritical ischemia where a non-invasive vascular examination was performed.	Patients with a DFU and subcritical ischemia (PEDIS-P = 2) where a non-invasive vascular examination (foot pulses, ABI, toe pressure, TcPO2, arterial Doppler exam) was performed.	Patients with a DFU and with subcritical ischemia (PEDIS-P = 2).
Proportion of patients with a DFU and critical ischemia where a non-invasive vascular examination was performed.	Patients with a DFU and critical ischemia (PEDIS-P = 3) where a non-invasive vascular examination (foot pulses, ABI, toe pressure, TcPO2, arterial Doppler exam) was performed.	Patients with a DFU and with critical ischemia (PEDIS-P = 3).
Proportion of patients with a DFU where an arterial duplex exam was performed.	Patients with a DFU where an arterial duplex exam was performed.	Patients with a DFU.
Proportion of patients with a DFU where a diagnostic angiography was performed.	Patients with a DFU where a diagnostic angiography was performed.	Patients with a DFU.
Proportion of patients with a DFU without PAD where an arterial duplex exam was performed.	Patients with a DFU and without PAD (PEDIS-P = 1) where an arterial duplex exam was performed.	Patients with a DFU and without PAD (PEDIS-P = 1).
Proportion of patients with a DFU without PAD where a diagnostic angiography was performed.	Patients with a DFU and without PAD (PEDIS-P = 1) where a diagnostic angiography was performed.	Patients with a DFU and without PAD (PEDIS-P = 1).
Proportion of patients with a DFU and subcritical ischemia where an arterial duplex exam was performed.	Patients with a DFU and subcritical ischemia (PEDIS-P = 2) where an arterial duplex exam was performed.	Patients with a DFU and subcritical ischemia (PEDIS-P = 2).

Appendix 1.2. Continued

VASCULAR EXAMINATIONS		
Proportion of patients with a DFU and subcritical ischemia where a diagnostic angiography was performed.	Patients with a DFU and subcritical ischemia (PEDIS-P = 2) where a diagnostic angiography was performed.	Patients with a DFU and subcritical ischemia (PEDIS-P = 2).
Proportion of patients with a DFU and critical ischemia where an arterial duplex exam was performed.	Patients with a DFU and critical ischemia (PEDIS-P = 3) where an arterial duplex exam was performed.	Patients with a DFU and critical ischemia (PEDIS-P = 3).
Proportion of patients with a DFU and critical ischemia where a diagnostic angiography was performed.	Patients with a DFU and critical ischemia (PEDIS-P = 3) where a diagnostic angiography was performed.	Patients with a DFU and critical ischemia (PEDIS-P = 3).
REVASCULARIZATION		
Proportion of patients with a DFU that underwent a revascularization of the lower limbs.	Patients with a DFU that underwent an endovascular revascularization or open bypass surgery.	Patients with a DFU.
Proportion of patients with a DFU without PAD that underwent a revascularization of the lower limbs.	Patients with a DFU and without PAD (PEDIS-P = 1) that underwent an endovascular revascularization or open bypass surgery.	Patients with a DFU and without PAD (PEDIS-P = 1).
Proportion of patients with a DFU and subcritical ischemia that underwent a revascularization of the lower limbs.	Patients with a DFU and subcritical ischemia (PEDIS-P = 2) that underwent an endovascular revascularization or open bypass surgery.	Patients with a DFU and subcritical ischemia (PEDIS-P = 2).
Proportion of patients with a DFU and critical ischemia that underwent a revascularization of the lower limbs.	Patients with a DFU and critical ischemia (PEDIS-P = 3) that underwent an endovascular revascularization or open bypass surgery.	Patients with a DFU and critical ischemia (PEDIS-P = 3).

Appendix 1.2. Continued

REVASCULARIZATION		
Proportion of patients with a DFU and a history of a previous revascularization that underwent a revascularization of the lower limbs.	Patients with a DFU and a history of a previous revascularization that underwent an endovascular revascularization or open bypass surgery.	Patients with a DFU and a history of a previous revascularization of the lower limbs.
Proportion of patients with a DFU that underwent an endovascular revascularization of the lower limbs.	Patients with a DFU that underwent an endovascular revascularization.	Patients with a DFU and known revascularization type.
Proportion of patients with a DFU that underwent a revascularization by open bypass surgery.	Patients with a DFU that underwent a revascularization by open bypass surgery.	Patients with a DFU and known revascularization type.
Proportion of patients with a DFU that underwent a revascularization at aortoiliac level.	Patients with a DFU that underwent a revascularization at aortoiliac level.	Patients with a DFU and known revascularization level.
Proportion of patients with a DFU that underwent a revascularization at femoropopliteal level.	Patients with a DFU that underwent a revascularization at femoropopliteallevel.	Patients with a DFU and known revascularization level.
Proportion of patients with a DFU that underwent a revascularization at infrapopliteal level.	Patients with a DFU that underwent a revascularization at infrapopliteal level.	Patients with a DFU and known revascularization level.

Appendix 1.2. Continued

ORTHOPAEDIC SURGERY		
Proportion of patients with a DFU that underwent minor amputation.	Patients with a DFU that underwent minor amputation.	Patients with a DFU.
Proportion of patients with a DFU that underwent major amputation.	Patients with a DFU that underwent major amputation.	Patients with a DFU.
Proportion of patients with a DFU that underwent surgical offloading.	Patients with a DFU that underwent surgical offloading.	Patients with a DFU.
Proportion of patients with a DFU that underwent Charcot surgery.	Patients with a DFU that underwent Charcot surgery.	Patients with a DFU.
SECONDARY PREVENTION		
Proportion of patients with a healed DFU for which podiatric follow-up was foreseen after resolution of the index foot problem.	Patients with a healed DFU for which podiatric follow-up was foreseen after resolution of the index foot problem.	Patients with a healed DFU at the end of the follow-up period.
Proportion of patients with a DFU where the podiatrist was involved in diagnostic procedures aimed at secondary prevention.	Patients with a DFU where the podiatrist was involved in diagnostic procedures aimed at secondary prevention.	Patients with a DFU.
Proportion of patients with a healed DFU where the podiatrist was involved in fitting of preventive footwear.	Patients with a healed DFU where the podiatrist was involved in fitting of preventive footwear.	Patients with a healed DFU at the end of the follow-up period.

Appendix 1.2. Continued

SECONDARY PREVENTION		
Proportion of patients with a healed DFU where adapted footwear for prevention was provided during this audit.	Patients with a healed DFU where adapted footwear for prevention was provided during this audit.	Patients with a healed DFU at the end of the follow-up period.
Proportion of patients with a healed DFU where adapted footwear for prevention was provided less than 2 years ago.	Patients with a healed DFU where adapted footwear for prevention was provided less than 2 years ago.	Patients with a healed DFU at the end of the follow-up period.
Proportion of patients with a healed DFU where a pair of orthopedic shoes was provided.	Patients with a healed DFU where a pair of orthopedic shoes was provided.	Patients with a healed DFU where adapted footwear for prevention was provided during this audit.
Proportion of patients with a healed DFU where 2 or more pairs of orthopedic shoes were provided.	Patients with a healed DFU where 2 or more pairs of orthopedic shoes were provided.	Patients with a healed DFU where adapted footwear for prevention was provided during this audit.
Proportion of patients with a healed DFU where a pair of semi-orthopedic shoes with individualized insoles was provided.	Patients with a healed DFU where a pair of semi-orthopedic shoes with individualized insoles was provided.	Patients with a healed DFU where adapted footwear for prevention was provided during this audit.
Proportion of patients with a healed DFU where 2 or more pairs of semi-orthopedic shoes with individualized insoles were provided.	Patients with a healed DFU where 2 or more pairs of semi-orthopedic shoes with individualized insoles were provided.	Patients with a healed DFU where adapted footwear for prevention was provided during this audit.
Proportion of patients with a healed DFU where a pair of semi-orthopedic shoes without individualized insoles was provided.	Patients with a healed DFU where a pair of semi-orthopedic shoes without individualized insoles was provided.	Patients with a healed DFU where adapted footwear for prevention was provided during this audit.
Proportion of patients with a healed DFU where 2 or more pairs of semi-orthopedic shoes without individualized insoles were provided.	Patients with a healed DFU where 2 or more pairs of semi-orthopedic shoes without individualized insoles were provided.	Patients with a healed DFU where adapted footwear for prevention was provided during this audit.

Appendix 1.2. Continued

SECONDARY PREVENTION		
Proportion of patients with a healed DFU where pairs of separately prescribed insoles for off-the-rack shoes were provided.	Patients with a healed DFU where pairs of separately prescribed insoles for off-the-rack shoes were provided.	Patients with a healed DFU where adapted footwear for prevention was provided during this audit.
Proportion of patients with a healed DFU where 2 or more pairs of separately prescribed insoles for off-the-rack shoes were provided.	Patients with a healed DFU where 2 or more pairs of separately prescribed insoles for off-the-rack shoes were provided.	Patients with a healed DFU where adapted footwear for prevention was provided during this audit.
Proportion of patients with a healed DFU where footwear specifically adapted for indoor use was provided.	Patients with a healed DFU where footwear specifically adapted for indoor use was provided.	Patients with a healed DFU where adapted footwear for prevention was provided during this audit.
Proportion of patients with a healed DFU where footwear specifically adapted for indoor use was provided less than 2 years ago.	Patients with a healed DFU where footwear specifically adapted for indoor use was provided less than 2 years ago.	Patients with a healed DFU where adapted footwear for prevention was provided during this audit.
Proportion of patients with a healed DFU where digital orthotics in silicone were provided.	Patients with a healed DFU where digital orthotics in silicone were provided.	Patients with a healed DFU at the end of the follow-up period.

Appendix 1.2. Continued

OUTCOME INDICATORS		
Proportion of patients with a DFU that were not lost to follow-up.	Patients with a DFU that were not lost to follow-up over a period of 6 months.	Patients with a DFU.
Proportion of patients with a DFU that deceased.	Patients with a DFU that deceased during the follow-up period.	Patients with a DFU that were not lost to follow-up over a period of 6 months.
Proportion of patients with a DFU that underwent a major amputation.	Patients with a DFU that underwent a major amputation.	Patients with a DFU that were not lost to follow-up over a period of 6 months.
Proportion of patients with a DFU, critical ischemia and deep or systemic infection that underwent a major amputation.	Patients with a DFU, critical ischemia (PEDIS-P = 3) and deep or systemic infection (PEDIS-I = 3 or 4) that underwent a major amputation	Patients with a DFU, critical ischemia (PEDIS-P = 3) and deep or systemic infection (PEDIS-I = 3 or 4) that were not lost to follow-up over a period of 6 months.
Proportion of patients with a DFU where the major amputation stump healed.	Patients with a DFU that underwent a major amputation and where the amputation stump healed.	Patients with a DFU that were not lost to follow-up over a period of 6 months that underwent a major amputation.
Proportion of patients with a DFU that are alive with conservation of the lower limb.	Patients with a DFU that did not decease and did not undergo a major amputation during the follow-up period.	Patients with a DFU that were not lost to follow-up over a period of 6 months.
Proportion of patients with a healed DFU.	Patients with a DFU that healed during the follow-up period.	Patients with a DFU that were not lost to follow-up over a period of 6 months.

Appendix 1.2. Continued

OUTCOME INDICATORS		
Proportion of patients with healed DFU that presented critical ischemia and deep or systemic infection	Proportion of patients with healed DFU that presented critical ischemia (PEDIS-P = 3) and deep or systemic infection (PEDIS-I = 3 or 4)	Patients of patients with critical ischemia (PEDIS-P = 3) and deep or systemic infection (PEDIS-I = 3 or 4) that were not lost to follow-up over a period of 6 months.
Proportion of patients with a healed DFU that underwent a minor amputation.	Patients with a healed DFU and that underwent a minor amputation during the follow-up period.	Patients with a DFU that were not lost to follow-up over a period of 6 months.
Proportion of patients with a healed DFU without amputation.	Patients with a healed DFU and that did not undergo a minor or major amputation during the follow-up period.	Patients with a DFU that were not lost to follow-up over a period of 6 months.
Proportion of patients with a healed DFU that relapsed.	Patients with a DFU that healed, but the index diabetic foot lesion relapsed during the follow-up period.	Patients with a DFU that were not lost to follow-up over a period of 6 months and where the DFU healed.
Proportion of patients with a chronic DFU.	Patients with a DFU that did not heal or that did not undergo a major amputation during the follow-up period.	Patients with a DFU that were not lost to follow-up over a period of 6 months.
Proportion of patients with a chronic DFU that presented critical ischemia and deep or systemic infection	Patients with a DFU that did not heal or that did not undergo a major amputation during the follow-up period, and that presented critical ischemia (PEDIS-P = 3) and deep or systemic infection (PEDIS-I = 3 or 4)	Patients with a DFU that presented critical ischemia (PEDIS-P = 3) and deep or systemic infection (PEDIS-I = 3 or 4), and that were not lost to follow-up over a period of 6 months.
Proportion of patients with a DFU where both feet were free of active diabetic foot lesions at the end of follow-up.	Patients with a DFU where both feet were free of active diabetic foot lesions at the end of follow-up.	Patients with a DFU.

Appendix to chapter 3

Appendix 3.1. References of included studies for formulating QIs in chapter 3

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Appendix to chapter 4

Appendix 4.1. Example of a personalized panelist rating sheet received by each stakeholder during the consensus method. The frequency of responses for each indicator is shown in bold in the top row. In the following example, two stakeholders rated the candidate QI "E.1" at 5, one stakeholder rated it at 6, one stakeholder rated it at 7, two stakeholders rated it at 8 and eight stakeholders rated it at 9. This particular stakeholder rated it at 9.

No.	Indicator	Appropriateness as indicator									Median	Level of appropriateness	Disagreement
		Highly inappropriate								Highly appropriate			
E.1	Proportion of people with a (history of) diabetic foot ulcer receiving patient education					**2**	**1**	**1**	**2**	**8**	9	A	NO
		1	2	3	4	5	6	7	8	9			
E.2a	Proportion of people with a history of peripheral neuropathy (PNP) receiving therapeutic footwear and/or custom-made insoles, or custom-made shoes							**2**	**5**	**7**	8,5	A	NO
		1	2	3	4	5	6	7	8	1			
E.2b	Proportion of people with a history of diabetic foot ulcer receiving optimization by plantar pressure measurements of their custom-made footwear and/or insoles					**1**		**2**	**6**	**5**	8	A	NO
		1	2	3	4	5	6	7	8	1			
E.3	Proportion of people with a (history of) diabetic foot ulcer treated within the context of a prevention management program for diabetic foot						**2**	**2**	**3**	**7**	8,5	A	NO
		1	2	3	4	5	6	7	8	9			

Appropriate (A): panel median of 7-9, without disagreement (NO)
Uncertain (U): panel median of 4-6 or any median with disagreement (YES)
Inappropriate (I): panel median of 1-3, without disagreement (NO)

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PUBLICATIONS

Flora Mbela Lusendi, An-Sofie Vanherwegen, Kris Doggen, Frank Nobels, and Giovanni A. Matricali. Evidence-Based Interventions for Identifying Candidate Quality Indicators to Assess Quality of Care in Diabetic Foot Clinics: A Scoping Review. BMC Public Health 24, no. 1 (April 10, 2024): 996. https://doi.org/10.1186/s12889-024-18306-2.

Flora Mbela Lusendi, An-Sofie Vanherwegen, Frank Nobels*, and Giovanni A. Matricali*. A Multidisciplinary Delphi Consensus to Define Evidence-Based Quality Indicators for Diabetic Foot Ulcer Care. European Journal of Public Health 34, no. 2 (April 3, 2024): 253–59. https://doi.org/10.1093/eurpub/ckad235.
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Flora Mbela Lusendi, Giovanni A. Matricali, An-Sofie Vanherwegen, Kris Doggen and Frank Nobels. Bottom-up Approach to Build a 'Precision' Risk Factor Classification for Diabetic Foot Ulcer Healing. Proof-of-Concept." Diabetes Research and Clinical Practice 191 (September 2022): 110028. https://doi.org/10.1016/j.diabres.2022.110028.

Wahid Rezaie, **Flora Mbela Lusendi**, Kris Doggen, Giovanni A. Matricali, and Frank Nobels. Health-related quality of life in patients with diabetic foot ulceration: study protocol for adaptation and validation of patient-reported outcome measurements (PROMs) in Dutch-speaking patients. BMJ Open. 2019 Dec 23;9(12):e034491.https://bmjopen.bmj.com/content/9/12/e034491

INTERNATIONAL CONFERENCES

Oral presentation at **9th International Symposium on the Diabetic Foot**, The Hague, Netherlands, May 10-13,2023

Creation of a 'precision prognostic classification' for diabetic foot ulcer healing with the use of a bottom-up approach

Poster presentation at **9th International Symposium on the Diabetic Foot**, The Hague, Netherlands, May 10-13,2023

Evidence-based quality indicators in diabetic foot care: the Belgian multidisciplinary expert panel opinion

Poster presentation at **8th International Symposium on the Diabetic Foot**, The Hague, Netherlands, May 21-25, 2019

Which ulcer and patient characteristics can guide clinicians in determining the risk of non-healing of a diabetic foot ulcer?

OTHER ORAL AND POSTER PRESENTATIONS

Poster presentation, Diabetes Liga symposium, 29 November 2023

Development of quality indicators for diabetic foot care: a mixed method approach

Oral presentation, Resident day, Orthopedie en Traumatologie service (IORT group), 16 June 2023

Identification of valid and multidimensional quality indicators in diabetic foot care, useful to study quality of care in diabetic foot clinics

Oral presentation, Departmental day, Development and regeneration, 16 February 2023

A bottom-up approach to build a “precision” risk-factor classification for diabetic foot ulcer healing. Proof-of-concept.

Oral presentation, EpiTuesday seminar at Sciensano, 14 February 2023

A bottom-up approach to build a “precision” risk-factor classification for diabetic foot ulcer healing. Proof-of-concept.

Oral presentation, Belgian Diabetic Foot Study Group, 19 September 2019.

Identification of valid and Multidimensional quality indicators in diabetic foot care, useful to study quality of care in diabetic foot clinics - Consensus method approach.

Oral presentation, IQED-Foot Expert group meeting, 8 May 2017

Scope of quality of care monitoring in the treatment of the diabetic foot (SquirmyFOOT)

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