Scientific report on clinical trials in the therapeutic area of wound treatment[1]

EXTRACT

Project: A24-61 Version: 1.0 Status: 11 Apr 2025 DOI: 10.60584/A24-61_en

[1] Translation of Chapters 1 to 7 of the rapid report A24-61 *Wissenschaftliche Ausarbeitung zu klinischen Studien im Therapiegebiet Wundbehandlung* (Version 1.0; Status: 11 April 2025). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Scientific report on clinical trials in the therapeutic area of wound treatment

Commissioning agency

Federal Joint Committee

Commission awarded on

7 May 2024

Internal Project No.

A24-61

DOI-URL

https://doi.org/10.60584/A24-61_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone:+49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Recommended citation

Institute for Quality and Efficiency in Health Care. Scientific report on clinical trials in the therapeutic area of wound treatment; Extract [online]. 2025 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A24-61_en.

Keywords

Endpoint Determination, Wound Healing, Clinical Trials as Topic

This report was prepared in collaboration with external experts on medical issues. According to §139 b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed *Form for disclosure of potential conflicts of interest* from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

The advisory role of the external expert included providing written answers to questions on topics such as clinical picture/consequences of the disease, treatment goals, patients in everyday German healthcare, treatment options, therapeutic needs and the state of medical practice. In addition, the expert was involved in further specific questions during the course of the project. The responsibility for the contents of the report lies solely with IQWiG.

External expert

- Robert Strohal, Feldkirch Regional Hospital, Department of Dermatology and Venereology, Feldkirch, Austria

Patient and family involvement

Patients or family members were consulted during the preparation of the report. Six persons participated in the discussion. Its aim was to obtain information on the following topics: the impact of the disease on everyday life and coping with the disease, as well as their wishes regarding treatment, including treatment goals, and their experiences and concerns with regard to treatment.

IQWiG would like to thank the participants for taking part in the discussion. They were not involved in the actual writing of the report.

IQWiG employees

- Bent Müller
- Tatjana Hermanns
- Heike Kölsch
- Philip Kranz
- Fabian Lotz
- Regine Potthast

Executive summary

On 7 May 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to prepare a scientific report on clinical trials in the therapeutic area of wound treatment, with a focus on evaluating outcomes.

Research question

The objectives of this report are

- to describe relevant chronic wound entities,
- to compile an overview of outcomes that are recorded in clinical trials on wound treatment, and to subsequently evaluate the respective operationalizations and the validity of the data collection instruments used, taking into account the wound entity where applicable,
- to identify other key study characteristics related to the respective outcomes, such as study duration and the need for blinding, and
- to systematically search for surrogate validation studies on the outcome of partial wound closure.

Methods

Information retrieval and evaluation

Wound entities, relevant outcomes, and other study characteristics

To describe relevant chronic wound entities, create an overview of outcomes, and identify key study characteristics, an exploratory search for publications was conducted in MEDLINE, the International HTA Database, and on the websites of the National Institute for Health and Care Excellence (NICE), Canada's Drug Agency (CDA), and the US Agency for Healthcare Research and Quality (AHRQ), among others. In addition, the websites of the G-BA, IQWiG, the Food and Drug Administration (FDA), and the European Medicines Agency (EMA) were searched.

Surrogate validation studies on the outcome of partial wound closure

A focused search for relevant surrogate validation studies to assess the validity of partial wound closure as a surrogate for patient-relevant outcomes was conducted in the following bibliographic databases: MEDLINE and Central. In addition, relevant reference lists and the websites of the G-BA, IQWiG, the FDA, and the EMA were reviewed.

Information synthesis

Description of relevant chronic wound entities

Based on the results of the exploratory search, an overview of the identified wound entities was created. Their frequency, epidemiology, causes, characteristic features, and specific treatments were described, and the individual entities were distinguished from one another on this basis.

Overview of outcomes in clinical trials

Based on the exploratory research, an overview of the outcomes regularly recorded in clinical trials on wound treatment was created. The respective operationalizations and the validity of the data collection instruments used were evaluated, taking into account the wound entity where applicable, and based on this, the suitability of these outcomes for a benefit assessment was assessed.

Identification of other key study characteristics with reference to the respective outcomes

Key requirements for studies in the area of wound treatment, such as study duration, study size, randomization, and the need for blinding, were described with reference to the respective outcomes. From this, principles for the planning and conduct of clinical trials in the therapeutic area of wound treatment were derived. In addition, the potential transferability of results from clinical trials on one wound entity to other wound entities was investigated.

Surrogate validation studies

Surrogate validation studies identified through a systematic literature search were reviewed for suitability using the Institute's General Methods. Based on the identified surrogate validation studies, an assessment was made as to whether the outcome of partial wound closure can be considered a valid surrogate for patient-relevant outcomes.

Results

Entities of chronic wounds

Relevant entities of chronic wounds were identified for this report. These include chronic wounds caused by an underlying disease that influences or prevents successful healing, such as diabetic foot ulcers and leg ulcers (venous leg ulcers, arterial leg ulcers, mixed arterial-venous leg ulcers). Other physical limitations that exist over a longer period of time (e.g., immobility) can also cause chronic wounds (pressure ulcers). Furthermore, chronic wounds can be caused by inflammation or tumour diseases, among other things, in which the wound no longer heals after surgery or the tumour itself breaks through the skin barrier.

Relevant outcomes in the therapeutic area of chronic wounds

The following outcomes are generally relevant to patients and should be routinely recorded in clinical trials in the therapeutic area of chronic wounds:

Mortality

Deaths should be regularly recorded, analysed, and reported in clinical trials on the treatment of chronic wounds.

Morbidity

Complete wound closure and prevention of recurrence – healing

Achieving complete and sustained wound closure corresponds to healing of the disease. Complete wound closure and thus complete healing of the wound is of the utmost importance to patients and is the primary treatment goal for most wound entities (except potentially in palliative treatment situations). This outcome is therefore relevant to patients and should be recorded in every clinical trial in this therapeutic area.

In order to assess the sustainability of complete wound closure, all randomized patients should be followed up for as long as possible, regardless of whether complete wound closure (possibly interim) has been achieved.

Partial wound closure – substantial improvement in the patients' life situation

Complete wound closure is usually the primary treatment goal. However, in some situations, partial wound closure can also mean a substantial improvement in the patient's life situation.

The advantage of one intervention over a control intervention in terms of reducing the size of a wound area alone is not sufficient to justify its benefit. For example, without knowledge and evaluation of the specific wound characteristics, it is unclear what a 50 percent reduction in wound area means for patients and whether this change is perceived as a noticeable improvement in their life situation. In order to derive a benefit, it must therefore be sufficiently certain that partial wound closure has a direct impact on patient-relevant aspects. In particular, these include improvements in health-related quality of life, activities of daily living, pain, and a noticeable change in a stressful wound characteristic (e.g., ulceration) that goes beyond size. To this end, the achievement of partial wound closure in clinical trials can be linked to the achievement of an improvement in at least one directly patient-relevant outcome within a specific time frame. This increases the likelihood that the partial wound closure observed under the intervention is relevant to the patient, as it is actually accompanied by an improvement in outcomes that are directly noticeable to patients. Furthermore, linking partial wound closure to health-related quality of life or activities of daily living also takes into account potentially burdensome aspects of wound care, such as the number of wound dressing changes.

Pain

In patients with chronic wounds, pain is often a combination of chronic pain and acute pain (e.g., when changing wound dressings). There are no objective measures for recording pain

intensity. Therefore, pain needs to be recorded as a patient-reported outcome. This should be done using a validated, indication-specific, or generic instrument. An indication-specific instrument generally allows for a more sensitive measurement of changes and is easier to interpret. It is therefore generally preferable to a generic instrument.

(Disease-related) hospitalization

In studies on the treatment of chronic wounds, hospitalization should be recorded as disease-related hospitalization, i.e., hospitalization due to chronic wounds. To ensure that hospitalization is attributable to the chronic wound, events should be adjudicated adequately and transparently using a predefined list of wound-related complications (wound bleeding, wound infections, etc.). This allows potential differences in the healthcare setting to be addressed in multinational studies.

Amputation

Patients with chronic wounds on the lower legs and feet (leg ulcer, diabetic foot ulcer) have an increased risk of amputation during the course of their illness. The outcome of amputations should be recorded in clinical trials on chronic wounds of the extremities.

Wound infection

Due to the classic signs of inflammation (redness, overheating, swelling, pain, and limited function), wound infection is usually noticeable to patients and can also lead to serious complications such as life-threatening sepsis in advanced stages. The recording of the outcome of wound infection must be based on these clinical signs and symptoms that are noticeable to patients and should be carried out using established systems for the respective wound entities.

Restrictions on activities of daily living and social participation

Outcomes relating to activities of daily living and social participation are relevant to patients, but are rarely recorded in clinical trials in the therapeutic area of chronic wounds.

The limitations of patients in these two areas can result in particular from pain, limited mobility, and embarrassment due to wound odour/exudate.

The outcome of activities of daily living is recorded in order to assess a person's ability to perform basic and instrumental daily tasks independently. Basic activities include bathing/showering, personal hygiene, dressing, using the toilet, and eating. Instrumental activities include more complex activities necessary for independent living, such as preparing meals or shopping.

There is no uniform, narrow definition of social participation in the literature. Various forms of social participation are described, including social bonding (relationships with people), informal social participation (joint activities with other people), and volunteer work.

In the therapeutic area of chronic wounds, both activities of daily living and social participation should be recorded using appropriate, validated instruments. Since the goals for social participation or activities of daily living can be very heterogeneous for patients with chronic wounds, when recording these outcomes, it may be useful to agree on individual goals for each patient and to define the descriptions of the individual goal attainment levels in consultation between the patient and the doctor. The outcomes of wound odour and exudate (increase in the exudate volume and/or change in colour) are alone insufficient to justify a benefit based solely on direct measurement of the odour or exudate. However, they are relevant for patients if the occurrence of these events leads to social isolation and limited participation in social life. These complex relationships cannot be reflected by simply asking about odour perception alone. These outcomes must therefore always be assessed in relation to the resulting limitations on the patients' activities of daily living or social participation.

Health state

The outcome of health state is relevant to patients. In studies on the treatment of chronic wounds, the Visual Analogue Scale (VAS) of the EQ-5D questionnaire can be used to record health state.

Health-related quality of life

Outcomes relating to health-related quality of life are patient-relevant. In general, these should be recorded using validated instruments that are suitable for use in clinical trials and have been evaluated accordingly. Both generic and disease-specific instruments for recording health-related quality of life are available in German.

Adverse effects

In a clinical trial for the treatment of chronic wounds, adverse events (AEs) that occur during the course of the trial must be documented according to an established system (e.g., Medical Dictionary for Regulatory Activities [MedDRA]), regardless of whether every AE is to be recorded or only a predefined selection based on content or severity. In any case, it is necessary to record all serious adverse events (SAEs) and all AEs that have led to discontinuation of treatment. For these higher-level AE outcomes, the overall rates (patients with events) should be presented in each case.

Study characteristics

Clinical trials in the therapeutic area of chronic wounds should be conducted as RCTs. To answer questions in this area, RCTs with an adaptive design are also conceivable, which make

it possible to respond to interim findings obtained during the study and to make adjustments for the further course of the study. When conducting a study, patients, study staff, and outcome assessors should be blinded. If blinding is not performed – for example because the measures used to maintain blinding potentially jeopardize the transferability of the results to the relevant healthcare context – it should at least be ensured that the mandatory participant information and education about the potential benefits or harms of the treatment options used in the study is provided in a neutral manner. This is particularly relevant for subjectively assessed outcomes such as health-related quality of life. If more than one wound entity or wounds with different characteristics are considered in a study, it is necessary to define the different entities as a stratification factor and to plan appropriate subgroup analyses.

A necessary prerequisite for meaningful studies is that the respective treatments in the study arms are clearly defined in the study protocol and, as far as possible, differ between the study arms only in the test or control intervention. The control treatment in a study should reflect the standard treatment for the treatment stage of the respective chronic wound according to the current state of scientific knowledge. When planning the study, it should be considered that wound treatment during the study may in most cases consist of a combination of different wound type- and phase-specific interventions or treatment breaks. The study protocol should therefore specify as precisely as possible the treatment algorithm for the controlled continuation of treatment after the initial study treatment. Accordingly, pathways for optimal treatment management should be defined that, in addition to the test and control interventions, ensure largely standardized and phase-appropriate treatment of all included patients after the initial study treatment. The use of concomitant treatments for wound treatment and for the treatment of the underlying diseases causing the chronic wounds should also be comparable between the study arms, correspond to current everyday care, and be specified in the study protocol.

In order to obtain meaningful results, a sufficiently long treatment period, including a subsequent follow-up period for the outcomes recorded, is necessary. The minimum duration of a clinical trial in the therapeutic area of chronic wounds is variable and should be selected depending on the treatment goal or the outcomes considered. In studies with the treatment goal of healing (complete wound closure), the duration should be based on the expected time to sustainable healing. A minimum total study duration of 6 months is assumed for this purpose. For studies with the treatment goal of substantial improvement (partial wound closure coupled with an outcome directly relevant to the patient), shorter total study durations may be sufficient, but should not be less than 3 months. When investigating interventions with short-term treatment goals (such as infection resolution or pain reduction), the overarching goal for the use of wound treatment products must be considered, namely to contribute to complete wound healing or at least to achieve a substantial improvement in the patient's life situation. It cannot be ruled out that phase-specific interventions that are only

used for a short period of time and whose benefit is to be justified by short-term outcomes may have an influence on outcomes that can only be achieved later, such as complete wound closure. It is therefore not reasonable to derive the benefit of a test intervention for wound treatment solely on the basis of the short-term observed effect or to plan studies with a shortened study duration of less than 3 months.

In justified cases, the transfer of study results (e.g., from one wound entity to another; from one intervention to another) can be reviewed and, if necessary, carried out. The methodological approach to testing the transferability of evidence consists of using the evidence to demonstrate, on the basis of evidence on a partially modified question (e.g., different intervention; different population), that there is sufficient similarity in the effects relevant to benefits and harms. To this end, certain minimum criteria must be met in the processing of the available evidence. This includes defining the reference and target questions, conducting systematic information retrieval, and comprehensively processing the specific characteristics of the patients and chronic wounds in the study reports and publications relevant to the transfer for both the reference and target questions. The transfer of evidence is generally subject to a high degree of uncertainty. Therefore, studies should provide sufficiently large and consistent effects across multiple outcomes in order to answer the reference question.

Partial wound closure as a surrogate for patient-relevant outcomes

Based on systematic information retrieval, no valid surrogate validation study was identified for the outcome of partial wound closure as a surrogate for a patient-relevant outcome. However, this report presents a proposal for the planning of a surrogate validation study; after its completion, conclusions can be drawn about the validity of partial wound closure as a surrogate for other patient-relevant outcomes.

Conclusion

This report provides recommendations for the planning and conduct of healthcare-relevant studies in the therapeutic area of chronic wounds. Key points include the definition of a treatment protocol for the test and control interventions and for any concomitant treatments as well as the definition of an appropriate observation period. Even when investigating interventions with short-term treatment goals, a sufficiently long observation period should be planned in order to be able to rule out negative effects on the overarching treatment goal of complete wound healing or a substantial improvement in the patient's life situation with sufficient certainty.

Patients, study staff, and outcome assessors should be blinded. Mandatory participant information and education about the potential benefits or harms of the treatment options used in the study should be provided in a neutral manner. In addition to the outcome of

complete wound closure, the recording of patient-reported outcomes on morbidity, activities of daily living, social participation, health-related quality of life, and adverse effects is particularly important. Consistent implementation of these recommendations will substantially improve the evidence base for the treatment of chronic wounds and thus also the care of patients.

Complete wound closure is usually the primary treatment goal, but in some situations, partial wound closure can also mean a substantial improvement in the patient's life situation. However, the reduction in wound size alone is not usually sufficient to justify a benefit. For example, without knowledge and evaluation of the specific wound characteristics, it is unclear what a 50 percent reduction in wound area means for patients and whether this change is perceived as a noticeable improvement in their respective life situation. In order to derive a benefit, it must therefore be sufficiently certain that partial wound closure has a direct impact on patient-relevant aspects, in particular improvements in health-related quality of life, activities of daily living, pain, and a noticeable change in a distressing wound characteristic (e.g., ulceration) that goes beyond size. To this end, the achievement of partial wound closure in clinical trials can be linked to the achievement of at least one directly patient-relevant, temporally-associated event.

Suitable studies that examine the validity of the outcome of partial wound closure as a surrogate for patient-relevant outcomes and meet the requirements for a surrogate validation study are not yet available. This rapid report therefore presents a proposal for the planning of a surrogate validation study.

Table of contents

Page

Executive summary ..... **iv**
List of tables ..... **xiv**
List of figures ..... **xv**
List of abbreviations ..... **xvi**
1 Background **1**
2 Research question **2**
3 Course of the project **3**
3.1 Project timeline **3**
3.2 Specifications and changes during the course of the project **3**
4 Methods **5**
4.1 Information retrieval and evaluation **5**
4.1.1 Wound entities, relevant outcomes, and other study characteristics 5
4.1.2 Surrogate validation studies on the outcome of partial wound closure 5
4.1.2.1 Criteria for the inclusion of publications in the report 5
4.1.2.2 Focused information retrieval 5
4.2 Information synthesis **6**
4.3 Patient involvement and involvement of external experts **7**
5 Results **8**
5.1 Wound entities, relevant outcomes, and key study characteristics **8**
5.1.1 Results of exploratory information retrieval 8
5.1.2 Wound entities 8
5.1.2.1 Frequency of chronic wound entities 9
5.1.2.2 Characterization of chronic wound entities 12
5.1.2.3 Treatment of chronic wounds 14
5.1.3 Overview and evaluation of outcomes recorded in studies on chronic wounds 16
5.1.3.1 Mortality 18
5.1.3.2 Morbidity 18
5.1.3.2.1 Complete wound closure and prevention of recurrence – healing 18
5.1.3.2.2 Partial wound closure – substantial improvement in the patients' life situation 19
5.1.3.2.3 Pain 21

5.1.3.2.4 Hospitalization ... 22
5.1.3.2.5 Amputation ... 23
5.1.3.2.6 Wound infection ... 23
5.1.3.2.7 Debridement and wound dressing changes ... 24
5.1.3.2.8 Restrictions on activities of daily living and social participation ... 24
5.1.3.2.9 Health state ... 26
5.1.3.2.10 Health-related quality of life ... 26
5.1.3.2.11 Adverse effects ... 28
5.1.3.3 Combined outcomes in the therapeutic area of chronic wounds ... 29
5.1.3.4 Appropriate analyses ... 29
5.1.4 Key features for conducting studies in the area of chronic wounds ... 30
5.1.4.1 Randomization ... 30
5.1.4.2 Adaptive study design ... 31
5.1.4.3 Blinding ... 31
5.1.4.4 Patient population ... 34
5.1.4.5 Intervention, control treatments, and concomitant treatments ... 35
5.1.4.6 Study duration ... 35
5.1.4.7 Transferability of study results between wound entities or interventions ... 36
5.2 Surrogate validation studies on the outcome of partial wound closure ... 37
5.2.1 Focused information retrieval ... 38
5.2.1.1 Bibliographic databases ... 38
5.2.1.2 Additional sources of information and search techniques ... 39
5.2.2 Resulting study pool ... 40
5.2.3 Current evidence base and possible approach to surrogate validation of partial wound closure as a surrogate for patient-relevant outcomes ... 40
5.2.3.1 Definition and use of a surrogate outcome ... 40
5.2.3.2 Current evidence base on the validation of partial wound closure as a surrogate ... 40
5.2.3.3 General options for surrogate validation ... 41
5.2.3.4 Specific approach for validating partial wound closure as a surrogate ... 43
6 Discussion ... 47
7 Conclusion ... 51
References for English extract ... 52

List of tables

Page

Table 1: Overview of the prevalence of wound entities in Germany within different patient groups 9
Table 2: Outcomes recorded in studies on the treatment of chronic wounds 17

List of figures

Page

Figure 1: Results of the focused information retrieval from the bibliographic databases and the study selection for surrogate validations 39

List of abbreviations

Abbreviation	Meaning
AE	adverse event
AHRQ	Agency for Healthcare Research and Quality
AIDS	acquired immune deficiency syndrome
BPI-SF	Brief Pain Inventory-Short Form
CDA	Canada's Drug Agency
CONSORT	Consolidated Standards of Reporting Trials
CWIS	Cardiff Wound Impact Schedule
DFS-SF	Diabetic Foot Ulcer Scale Short Form
EMA	European Medicines Agency
EWMA	European Wound Management Association
FDA	Food and Drug Administration
FLQA-w	Freiburg Life Quality Assessment – Wound Module
FPQLI-WV	Ferrans and Powers Quality of Life Index – Wounds Version
GAS	Goal Attainment Scaling
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HCC	hepatocellular carcinoma
HIV	human immunodeficiency virus
ICD	International Statistical Classification of Diseases and Related Health Problems
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICW	Initiative for Chronic Wounds
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
NICE	National Institute for Health and Care Excellence
NRS	Numerical Rating Scale
PAOD	peripheral arterial disease
PCS	Physical Component Summary
PT	preferred term

Abbreviation	Meaning
PUSH	Pressure Ulcer Scale for Healing
RCT	randomized controlled trial
SAE	serious adverse event
SF-12	Short Form-12 Health Survey
SF-36	Short Form-36 Health Survey
SOC	system organ class
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SPVU-5D	Sheffield Preference-based Venous Ulcer-5D questionnaire
sPzW	Sonstige Produkte zur Wundbehandlung (other wound treatment products)
STE	surrogate threshold effect
SVR	sustained viral response
TILI	Therapeutic Index for Local Infections
VAS	Visual Analogue Scale
VLU-QoL	Venous Leg Ulcer Quality of Life
WWS	Würzburg Wound Score

1 Background

In Germany “Other wound treatment products” (“Sonstige Produkte zur Wundbehandlung“, sPzW) are one of three groups of products used for wound treatment that were legally defined in 2019. sPzW differ from dressings in that they promote wound healing through a pharmacological, immunological, or metabolic effect in the human body (see §31 (1a) Social Code Book (SGB) V). SPzW can become prescribable after their medical benefits have been reviewed by the Federal Joint Committee (G-BA) and they have been included in Annex V of the German Drug Directive. In accordance with further legislative changes that came into force in 2023, the G-BA advises manufacturers of sPzW in particular on the specific content of the documents and studies to be submitted, including patient-relevant outcomes.

Therefore, in accordance with §91 SGB V, the G-BA decided at its meeting on 7 May 2024 to commission the Institute for Quality and Efficiency in Health Care (IQWiG) to prepare a scientific report on clinical trials in the therapeutic area of wound treatment, focusing on an evaluation of the outcomes in accordance with §139b (1), Sentence 1, in conjunction with §139a (3) SGB V.

2 Research question

The objectives of this report are

- to describe relevant chronic wound entities,
- to compile an overview of outcomes that are recorded in clinical trials on wound treatment, and to subsequently evaluate the respective operationalizations and the validity of the data collection instruments used, taking into account the wound entity where applicable,
- to identify other key study characteristics related to the respective outcomes, such as study duration and the need for blinding, and
- to systematically search for surrogate validation studies on the outcome of partial wound closure.

3 Course of the project

3.1 Project timeline

On 7 May 2024, the G-BA commissioned IQWiG to prepare a scientific report on clinical trials in the therapeutic area of wound treatment, with a focus on evaluating the outcomes.

An external expert was involved in the project.

Between 24 June 2024 and 15 July 2024, affected patients were consulted in individual interviews in order to gain an impression of how they experience chronic wounds, what their experiences with treatment have been, and what they expect from treatment.

The preliminary rapid report, version 1.0, dated 7 January 2025, was published on the IQWiG website on 8 January 2025, and comments were invited. Written comments could be submitted until 28 January 2025. Unclear aspects of the written comments on the preliminary rapid report were discussed with the commenters in a scientific debate on 21 February 2025. The main arguments from the comments are acknowledged in Appendix C of the full version of the rapid report.

The present final rapid report includes the changes resulting from the hearing.

Following the hearing, IQWiG prepared this final rapid report, which were published on the IQWiG website four weeks after submission to the G-BA. The comments received on the preliminary rapid report and the minutes of the scientific debate were made available in a separate document, "Documentation of the hearing on the preliminary rapid report," on the IQWiG website at the same time as the final rapid report.

3.2 Specifications and changes during the course of the project

Final rapid report compared to the preliminary rapid report

In addition to editorial changes, the following specifications or changes have been made in the final rapid report:

- In Section 5.1.2.1, data on the prevalence of chronic wounds from the health insurance fund “DAK-Gesundheit” from 2017 to 2021 have been discussed and included in Table 1.
- In Section 5.1.2.2, a new section of text has been added on other chronic wounds with less common causes.
- In Section 5.1.2.2, the description of diabetic foot ulcers has been specified with regard to neuropathies.
- Section 5.1.2.2 addresses the use of the term "mixed arterial-venous leg ulcers".

- In Section 5.1.3.2.10, a description of the methodological approach for reviewing the identified instruments for recording health-related quality of life has been added. In addition, the “Wound-QoL” questionnaire has been included.
- Section 5.1.4 now describes the possibility of adaptive study designs with dynamic sample size calculation.
- In Section 5.1.4.3, the necessity of neutral participant information and education in unblinded studies has been added. In addition, the possibility of a justified omission of blinding in a study has been described, provided that blinding would jeopardize or prevent the achievement of the study objective or a reliable outcome assessment.
- Section 5.1.4.5 now specifies the procedure for determining test interventions, control treatments, and concomitant treatments in clinical trials.
- In Section 5.1.4.6, the importance of short-term treatment goals has been specified with regard to the overarching goal for the use of wound treatment products (complete wound healing) and classified with regard to the planning of the study duration.
- The publication Lammert 2024 has been included in the discussion (Chapter 6).
- Appendix C "Appraisal of the hearing on the preliminary rapid report" has been added (see full report).

4 Methods

This commission comprises a scientific report on clinical trials in the therapeutic area of wound treatment, with a focus on evaluating outcomes.

4.1 Information retrieval and evaluation

4.1.1 Wound entities, relevant outcomes, and other study characteristics

In order to describe relevant chronic wound entities, create an overview of outcomes, and identify key study characteristics, an exploratory search for publications was conducted in MEDLINE, the International HTA Database, and on the websites of the National Institute for Health and Care Excellence (NICE), Canada's Drug Agency (CDA), and the Agency for Healthcare Research and Quality (AHRQ), among others. In addition, the websites of the G-BA, IQWiG, the Food and Drug Administration (FDA), and the European Medicines Agency (EMA) were searched.

Particular attention was paid to systematic reviews and evidence-based guidelines. In order to reflect the current state of scientific knowledge, the selection was primarily limited to publications from 2021 onwards.

The search and selection of relevant publications was carried out by one researcher. The quality assurance of the results was carried out by a second researcher. The presentation in the report is limited to the specific results.

4.1.2 Surrogate validation studies on the outcome of partial wound closure

4.1.2.1 Criteria for the inclusion of publications in the report

Content

Studies were included in which the outcome of partial wound closure was validated as a surrogate for patient-relevant outcomes.

Publication period

There were no restrictions on the publication period.

Publication language

The publication had to be written in German or English.

4.1.2.2 Focused information retrieval

Focused information retrieval was carried out for relevant surrogate validations to assess the validity of partial wound closure as a surrogate for patient-relevant outcomes in accordance with the General Methods of the Institute [1] .

The following primary and secondary sources of information and search techniques were taken into account:

- Bibliographic databases
  - MEDLINE
  - Central
- Additional sources of information and search techniques
  - Review of reference lists
  - Websites of the G-BA, IQWiG, the FDA, and the EMA
  - Hearing on the preliminary rapid report

The relevant publications were selected in two steps. In the first step, publications that were clearly irrelevant were excluded based on their title and, where available, their abstract. In the second step, the full texts of the remaining, potentially relevant publications were obtained, on the basis of which a decision was then made as to whether to include them in the assessment [1] .

All selection steps were carried out independently by two researchers. Discrepancies were resolved through discussion between the two.

4.2 Information synthesis

Description of relevant chronic wound entities

Based on the results of the exploratory search, an overview of the identified wound entities was created. Their epidemiology, causes, characteristic features, and specific treatments were described, and the individual entities were distinguished from one another on this basis.

Overview of outcomes in clinical trials

Based on the exploratory search, an overview of the outcomes regularly recorded in clinical trials on wound treatment was created. The respective operationalizations and the validity of the data collection instruments used were evaluated, taking into account the wound entity where applicable, and the suitability of these outcomes for a benefit assessment was assessed on this basis.

Identification of other key study characteristics with reference to the respective outcomes

Key requirements for studies in the area of wound treatment, such as study duration, study size, randomization, and the need for blinding, were described with reference to the previously identified outcomes. From this, principles for the planning and conduct of clinical trials in the therapeutic area of wound treatment were derived. In addition, the potential

transferability of results from clinical trials on one wound entity to other wound entities was investigated.

Surrogate validation studies

Surrogate validation studies identified through a systematic literature search were reviewed for suitability using the General Methods of the Institute [1]. Based on the identified surrogate validation studies, an assessment was made as to whether the outcome of partial wound closure could be considered a valid surrogate for patient-relevant outcomes in accordance with the General Methods.

4.3 Patient involvement and involvement of external experts

The commission involved the participation of affected patients, who participated in six separate discussions, as well as external experts. An external expert was initially involved via a questionnaire and then, as the project progressed, via involvement in further specific questions. Following the publication of the preliminary rapid report, the involvement of clinical experts was ensured via a hearing.

5 Results

5.1 Wound entities, relevant outcomes, and key study characteristics

5.1.1 Results of exploratory information retrieval

The exploratory search for wound entities, relevant outcomes, and other study characteristics identified a total of 71 relevant documents [2-72]. These are considered in the following Sections 5.1.2 (wound entities), 5.1.3 (outcomes), and 5.1.4 (study characteristics).

5.1.2 Wound entities

A wound is defined as the loss of the barrier between the body and the environment due to the destruction of tissue on the external or internal surfaces of the body [4,21]. The cause is injury in which various layers of tissue of the skin or mucous membrane are damaged or severed. Wounds can be classified according to their shape and structure, but also according to the type of origin or by dividing them into acute and chronic wounds. In the following, the classification into acute and chronic wounds is used [12].

Acute wounds are caused by an immediate, often sudden event. Traumatic wounds are caused, for example, by accidents such as burns, contusions, punctures, or bites. These include abrasions, lacerations, cuts, puncture wounds, and burns [12]. Medical procedures such as incisions, punctures, laser treatments, or operations lead to iatrogenic wounds [69]. In most cases, these acute wounds heal without complications within a few weeks via an exudative, resorptive, proliferative (granulation), and reparative phase (epithelialization) [69].

Chronic wounds are characterized by impaired wound healing. The wound persists for a longer period of time and healing is very slow or does not occur at all and is associated with complications [71]. A chronic wound can develop from an initially acute wound. This can be caused, for example, by an infection of the acute wound or a disturbance in blood circulation and thus in the supply of blood to the affected area of the body [10,21,51]. In addition, chronic underlying diseases that impair homeostasis in the tissue, e.g., due to disturbed blood circulation, can be the cause of a chronic wound. Examples of this are diabetic foot ulcers in diabetes mellitus, leg ulcers in peripheral arterial disease (PAD), and chronic venous insufficiency. Other physical limitations that exist over a longer period of time (e.g., immobility) can also cause chronic wounds to develop [17,21].

There are different definitions of a chronic wound. While the German expert standard "Care of people with chronic wounds" defines wounds that show no tendency to heal within 4 to 12 weeks under professional treatment as chronic wounds [18], the guideline of the German Society for Wound Healing and Wound Treatment uses the definition of a lack of healing within 8 weeks [17].

The following sections first describe the frequency of different wound entities and then characterize them.

5.1.2.1 Frequency of chronic wound entities

In order to identify relevant wound entities, the documents included in the literature review were examined for information on the frequency of different wound entities. For this purpose, data on the prevalence of chronic wounds in the general population in Germany was used, although the literature criticizes these data as not being sufficiently reliable [34,42].

Table 1 shows examples of prevalence rates for chronic wounds from various sources. These rates are based on data from patients with statutory health insurance and from inpatient and outpatient facilities [34,42,55,56,73]. These refer to data of 2012 [34,42,56], from 2012 to 2018 [55] and most recently from 2017 to 2021 (analysis of data from the healthcare fund "DAK-Gesundheit", Tisch 24 [73]).

The prevalence figures reported below only provide an estimate of the frequency of chronic wounds in Germany. Analyses based on the total population were not identified during the information retrieval process.

Table 1: Overview of the prevalence of wound entities in Germany within different patient groups (multipage table)

Publication Population	Wound entity	Prevalence [95% CI]
Table 2024 [73][a, b]		
"DAK-Gesundheit" data for the period 2017 to 2021 (n = approx. 2.6 million insured persons) Extrapolation to the total population[c]	Total	1.3% [n/a; n/a]
Heyer 2016 [34][a]		
"BARMER GEK" from 2012 (n = 9,109,732)[d] Extrapolation to the total population[c]	Leg ulcer	0.70% [0.70%; 0.71%]
	▪ Arterial leg ulcer	0.07% [0.06%; 0.07%]
	▪ Venous leg ulcer	0.41% [0.41%; 0.42%]
	▪ Mixed (both venous and arterial ulcer diagnosis)	0.01% [0.01%; 0.01%]
	▪ Not specified	0.21% [0.21%; 0.21%]
	Diabetic foot ulcer	0.27% [0.26%; 0.27%]
	Pressure ulcer	0.18% [0.18%; 0.18%]
	Other (including pyoderma gangrenosum and gangrene)	0.03% [0.03%; 0.03%]
	Total	1.04% [1.03%; 1.05%]

Table 1: Overview of the prevalence of wound entities in Germany within different patient groups (multipage table)

Publication Population	Wound entity	Prevalence [95% CI]
Köster 2015[42][a]		
"AOK Hessen / KV Hessen" from 2012 (n = 277,462), extrapolated to the total population[c]	Leg ulcer	0.53% [n/a]
	Diabetic foot ulcer	0.23% [n/a]
	Pressure ulcer	0.20% [n/a]
	Post-traumatic wounds[e]	0.13% [n/a]
	Burns/chemical burns	0.01% [n/a]
	Other[f]	0.09% [n/a]
	Total	1.09% [n/a]
Raeder 2020 [55]		
Patients treated as inpatients in German nursing homes (n = 7662) with a mean age of 85 years	Leg ulcer	0.9% [0.7%; 1.2%]
	Diabetic foot ulcer	0.6% [0.4%; 0.8%]
	Pressure ulcer	4.0% [3.5%; 4.4%]
	Arterial leg ulcer[g]	1.0% [0.8%; 1.2%]
	Total	7.8% [7.2%; 8.4%]
Raeder 2019 [56]		
Patients treated on an outpatient basis by nursing services (n = 880) with a mean age of 78.5 ± 12.3 years	Leg ulcer	4.0% [2.9%; 5.5%]
	Diabetic foot ulcer	1.6% [1.0%; 2.7%] (read from figure)
	Pressure ulcer	4.6% [3.4%; 6.1%]
	Arterial leg ulcer[g]	1.9% [1.2%; 3.0%] (read from figure)
	Infected surgical wounds	1.0% [0.5%; 1.9%] (read from figure)
	Tumour wounds	0.2% [0%;0.7%] (read from figure)
	Total	11.5% [9.6; 13.8]

Table 1: Overview of the prevalence of wound entities in Germany within different patient groups (multipage table)

Publication Population	Wound entity	Prevalence [95% CI]
a. The data are based on the narrow definition used in the study to include patients in the analysis. This definition includes patients who had a relevant ICD-10 diagnosis and a wound-related intervention/prescription over several quarters of the year. b. Data on prevalence in the narrow definition were only available in this report for overall prevalence, but not for the respective wound entities. For the latter, only data in the broad definition were available, which cannot be compared with the other data from the other studies shown in the table, which is why they are not shown here. c. There may be multiple entries of wounds in individual patients if wounds are listed in the registry under several different underlying diseases. d. Only data from patients with an ICD-10 diagnosis in ≥ 2 quarters within 4 quarters (inpatient) or ≥ 1 quarter (outpatient) were used [34]. e. This includes, for example, open wounds, traumatic amputations, wounds due to endoprosthetics, and complications following surgical procedures. f. Inflammation, abscesses, and other infections, amputation wounds, and postoperative wounds in cases of malignant neoplasms. g. The publication does not mention the wound entity, but rather the underlying disease (PAD). This has been replaced in this table by the wound entity (arterial leg ulcer), although it remains unclear whether this group also included patients with mixed arterial-venous leg ulcers. CI: confidence interval; ICD: International Statistical Classification of Diseases and Related Health Problems; PAD: peripheral arterial disease		

In analyses based on health insurance data from 2012 for the general population, leg ulcers are the most common type of chronic wound [34,42], followed by diabetic foot ulcers [34,42] and pressure ulcers [34,42]. Post-traumatic chronic wounds [42] and other wounds such as inflammations, abscesses, amputation wounds, and post-operative wounds [34,42] are reported less frequently [34,42].

The prevalence of chronic wounds increases with age. While a prevalence of chronic wounds of 0.8% ([34] Köster 2015 [42]) was determined for the 50- to 59-year-old age group, these values were 5.79% for 80- to 89-year-olds [34,42]. The prevalence also varies depending on the age of the patient within the individual wound entities. Köster 2015 reports values for leg ulcers and pressure ulcers of 0.6% and 0.09% respectively for 50- to 59-year-olds and 3.26% and 1.41% for 80- to 89-year-olds [42].

Based on the population of patients in inpatient care facilities (average age of 85) or patients receiving outpatient care (average age of 78.5 ± 12.3), the prevalence of pressure ulcers is 4.0% and 4.6%, respectively. This is shown by studies involving 7405 and 880 patients, respectively [55,56].

5.1.2.2 Characterization of chronic wound entities

The following section characterizes the most common chronic wound entities presented in Table 1. In addition, other, rarer causes of chronic wounds are described.

Leg ulcer (ulcus cruris)

A leg ulcer is colloquially referred to as an "open leg". It is caused by impaired blood circulation in the legs due to venous dysfunction (venous leg ulcer) or arterial circulatory disorder (arterial leg ulcer) [18]. There are also cases in which both venous and arterial components are present; these are referred to as mixed arterial-venous leg ulcers or mixed leg ulcers [15,17,18]. It should be noted that the term "mixed leg ulcer" is sometimes viewed critically [74], as it usually does not take into account the different stages or degrees of severity of the respective clinical pictures (venous dysfunction, arterial circulatory disorder) and thus the pathophysiology of the wounds.

Venous leg ulcer (ulcus cruris venosum)

Venous leg ulcers are caused by chronic venous insufficiency, which is either due to reflux, vascular obstruction, or a combination of both. This prevents sufficient blood from returning to the heart [15]. As a result, fluid accumulates in the lower legs, causing them to swell. The pressure this creates in the tissue damages the blood vessels, reduces blood flow to the skin, and promotes inflammatory reactions. Venous leg ulcers primarily occur in the ankle area and on the front of the lower leg [15].

Arterial leg ulcer (ulcus cruris arteriosum)

The cause of an arterial leg ulcer is PAD, which is promoted by various risk factors (e.g., diabetes mellitus, hypertension, smoking) and leads to an insufficient supply of oxygen and nutrients to the tissue [18]. The symptoms of PAD include exercise-induced muscle pain, which can develop into pain at rest as the disease progresses [21]. The skin on the affected extremities feels cool due to the lack of blood flow, injuries heal less well and can become chronic wounds that also affect deeper skin structures and muscles [17].

Mixed arterial-venous leg ulcer (ulcus cruris mixtum)

Mixed arterial-venous leg ulcers are leg ulcers in patients who suffer from both chronic venous insufficiency and PAD [15,21]. Symptoms of both venous and arterial ulcers occur to varying degrees. The severity of both diseases is determined during diagnosis [15,17].

Diabetic foot ulcer

A diabetic foot ulcer is a chronic wound on the foot that occurs in people with diabetes mellitus [18]. Long-term diabetes mellitus leads to damage to the blood vessels and consequently impairs blood circulation. The risk of developing PAD is increased [11,21]. Patients often also suffer from nerve damage (neuropathy), which is associated with reduced

or lost sensitivity to pain, meaning that affected patients do not notice pressure on their feet caused by unsuitable footwear, for example [17,21,24]. This can lead to pressure points, which can develop into small wounds that become increasingly larger and deeper if not detected and treated early on [17]. Due to the chronically elevated blood sugar levels associated with diabetes mellitus, wound healing disorders with inflammation also occur.

Pressure ulcers

Pressure ulcers primarily affect patients with permanently very limited mobility and/or chronic bedriddenness [21]. The underlying medical causes leading to bedriddenness vary. These can include advanced age, multimorbidity, paraplegia, incurable cancer, obesity, or condition after surgery [25,30].

A pressure ulcer is localized damage to the skin and/or underlying tissue caused by pressure or pressure combined with shear forces [25]. Depending on the type of tissue, tolerance to sustained pressure can vary and can also be influenced by factors such as blood circulation, age, and comorbidities [25]. Pressure ulcers usually develop over bony prominences, e.g., the ischial tuberosity, sacrum, coccyx, and heel [21,25]. Pressure ulcers can be caused by pressure from the patient's own weight on the affected areas of the body, but also by medical devices [25]. The problem is that if a pressure ulcer is not detected and treated early, it can cause damage to the deep layers of the skin, as well as to muscles, tendons, and organs [30]. This can result in large, very deep, and painful wounds.

Other causes of chronic wounds

In addition to the above-mentioned forms of chronic wounds, other rare causes of chronic wounds are described. The consensus document of the European Wound Management Association (EWMA) lists inflammation, infection, oncological diseases, and genetic factors, among others, as causes that can lead to chronic wounds [75].

In acute wounds, inflammatory reactions, e.g., due to infection of the wound, can disrupt wound healing and lead to the development of a chronic wound [72]. In addition, chronic wounds can occur in chronic inflammatory diseases such as vasculitis, in which autoimmune processes lead to inflammation of the blood vessels [21]. Pyoderma gangrenosum, a destructive ulcerative neutrophilic dermatosis of unknown aetiology, is also associated with autoinflammatory or inflammatory diseases such as inflammatory bowel disease or rheumatoid arthritis [2,21].

Various genetic disorders can be accompanied by chronic wounds. Epidermolysis bullosa, for example, is characterized by the formation of blisters and erosions on the skin, which can develop into chronic wounds [76]. Klinefelter syndrome can lead to phlebothrombosis, which in turn can cause chronic wounds such as leg ulcers [21].

Oncological diseases in which the wound does not heal after surgery or the tumour itself breaks through the skin barrier can also lead to chronic wounds and malignant wounds [14]. Other causes of chronic wounds include long-term immunosuppressive therapy such as chemotherapy and glucocorticoids [21,72]. In some cases, however, the disease-specific causes of a chronic wound are unknown, complicating treatment and thus wound healing.

5.1.2.3 Treatment of chronic wounds

Guidelines

Several German and international guidelines and recommendations deal with chronic wound entities and recommendations for wound treatment [2,14-18,30]. In addition to recommendations dealing with various forms of chronic wounds [18], guidelines are available on diseases that can lead to chronic wounds or specific wound entities [2,14-17,30].

The guidelines show that there are many different approaches to treating chronic wounds. They mention numerous medical methods and a large number of different medical devices that are used to treat chronic wounds (e.g., wound dressings with specific properties, vacuum wound sealing, hyperbaric oxygen therapy).

In addition to recommendations for wound treatment, several guidelines present the literature on which the recommendations are based [3,14,17,18,25]. The fact that, based on this literature, the recommendations for wound treatment are mostly formulated exclusively as expert opinions (consensus-based) leads to the conclusion that data from high-quality studies, such as randomized controlled trials (RCTs), are not sufficiently available for all methods, procedures, and wound entities and/or that the evidence base is heterogeneous. Accordingly, most guidelines are S1 guidelines (pyoderma gangrenosum [2], cross-section-specific pressure ulcer treatment and prevention [30]) or S2k guidelines (venous leg ulcers [15], burn wounds [16]).

General principles for the treatment of chronic wounds

In accordance with the recommendations of the guidelines, the procedure for treating chronic wounds can be described as follows [14,17,18,25]:

- Clarification of the cause of the chronic wound

  In order to heal a chronic wound, it is essential, according to the guidelines, to determine the cause of the chronic wound [18,25]. In the case of chronic wounds that have developed due to a chronic underlying disease, the underlying cause should be clarified and guideline-compliant treatment initiated, as this can influence the healing of the chronic wound [17].

- Characterization of the wound

  According to the guidelines, the treatment to be initiated depends on the condition of the wound, which should be determined based on factors such as the size and depth of the wound, its location, the amount of exudate, the type of tissue affected, and the intensity of pain [17].

  The use of instruments to assess the severity of chronic wounds is evaluated differently in the guidelines. The S3 guideline on topical treatment for slow-healing and/or chronic wounds states that numerous instruments have been developed to determine the severity of a wound, but that these lack the necessary reliability or validity or have not been sufficiently tested, and therefore no recommendation for the use of specific instruments can be derived [17]. For pressure ulcers, the international guideline [25] recommends the use of a wound classification system (e.g., National Pressure Ulcer Advisory Panel / European Pressure Ulcer Advisory Panel [NPUAP/EPUAP] or International Statistical Classification of Diseases and Related Health Problems [ICD-11]). However, these guidelines do not clearly advocate any particular classification system [25]. The degree of thermal burns (Grade 1 to 4) is assessed in accordance with the S2k guidelines for the treatment of thermal wounds using a classification of the depth of the burn [16].

- Wound cleansing and debridement

  In accordance with the guidelines, chronic wounds in particular, which may contain avital tissue, coatings, contaminants, exudate residues, and/or pathogens, should first be cleaned [17]. Mechanical, surgical, autolytic, enzymatic, or biological debridement is used for this purpose [25]. According to the guidelines, the method to be used depends, among other things, on the wound entity, wound severity, exudate volume, and whether or not the wound is infected [17,25].

- Wound coverage / promoting wound healing / wound closure

  Wound coverage is recommended in the guidelines for chronic wounds, such as leg ulcers, diabetic foot ulcers, and pressure ulcers [17,25]. It has essential functions in the treatment of chronic wounds; it is intended to create a wound environment conducive to healing and to protect the wound from further damage, for example from contamination, pathogens, or physical effects (pressure, chafing). Numerous wound dressings containing medication are available [3,17]. However, the recommendations for the use of these wound dressings are often based on a weak evidence base [17]. For particularly large or deep wounds, the guidelines sometimes recommend additional physical measures (e.g., hyperbaric oxygen therapy) [17]. For severe wounds that do not heal with conservative treatment, the guidelines recommend considering the possibility

of secondary surgical skin closure using autologous skin replacement after professional wound conditioning [16,17,25].

5.1.3 Overview and evaluation of outcomes recorded in studies on chronic wounds

Based on the publications identified in the exploratory search [3,5,9,31,33,35,43,46-50,52,57-59,61,66,68,77], an overview of the outcomes that are regularly recorded in clinical trials on the treatment of chronic wounds was created. The identified outcomes are presented in Table 2, with examples of operationalizations used. The description, including the assessment of the patient relevance of these outcomes, is provided in the following text.

Table 2: Outcomes recorded in studies on the treatment of chronic wounds

Outcome category **Outcome**	**Examples of operationalizations**	**Patient relevance**
Mortality		
Death	▪ Death rate	●
Morbidity		
Complete wound closure	▪ Re-epithelialization without the need for drainage or dressing	●
Recurrence	▪ Rate at end of study	●
Partial wound closure	▪ Percentage decrease in wound length, wound circumference, wound depth, wound area, and/or wound volume, among other things (based in part on questionnaires)	○
Pain	▪ Measured using simple scales (e.g., VAS) ▪ Measured using complex instruments (e.g., BPI-SF)	●
Wound infection	▪ Clinical signs of infection ▪ Resolution of infection	●
Wound odour	▪ VAS ▪ Yes/no question	○
Exudate	▪ Reduction in exudate volume	○
Hospitalization	▪ Disease-related hospitalization	●
Amputation	▪ Major amputation ▪ Minor amputation	●
Debridement	▪ Time until successful debridement ▪ Number of debridements required	○
Wound dressing changes	▪ Number of dressing changes	○
Health state	▪ EQ-5D VAS	●
Activities of daily living / social participation	▪ Time until normal daily activity can be resumed	●
Health-related quality of life	▪ Validated indication-specific or generic instrument	●
Adverse effects	▪ Including allergic skin reactions, cellulitis ▪ Systematically collected using MedDRA	●

● Patient-relevant
○ Generally not sufficient on its own to justify a benefit

BPI-SF: Brief Pain Inventory-Short Form; MedDRA: Medical Dictionary for Regulatory Activities; VAS: Visual Analogue Scale

The outcomes presented in Table 2 are described below and evaluated in terms of their patient relevance in the therapeutic area of chronic wound treatment. In this context, patient relevance refers to how a patient feels, how well they can perform their functions and activities, and whether they survive [78]. Both the intended and unintended effects of the interventions are taken into account, allowing an assessment of the influence on the following patient-relevant outcomes to determine disease- and treatment-related changes:

- Mortality
- Morbidity
- Health-related quality of life
- Adverse effects

5.1.3.1 Mortality

Survival is a patient-relevant outcome. Deaths should be systematically recorded, analysed, and reported in clinical trials on the treatment of chronic wounds.

5.1.3.2 Morbidity

5.1.3.2.1 Complete wound closure and prevention of recurrence – healing

Achieving complete and sustained wound closure corresponds to healing of the disease. Complete wound closure and thus complete healing of the wound is of the utmost importance to affected patients and is the primary treatment goal for most wound entities (except potentially in palliative treatment situations). This outcome is therefore relevant to patients and should be recorded in every clinical trial in this therapeutic area.

Complete wound closure is defined differently in studies on the treatment of chronic wounds, but usually includes complete epithelialization of the wound surface. The FDA defines the outcome of complete wound closure in chronic wounds as re-epithelialization without the need for drainage or dressing, confirmed at two consecutive study visits two weeks apart [79]. It is not decisive whether the wound closure was achieved through healing or whether it was performed surgically. This operationalization is adequate.

In addition, in clinical trials in the therapeutic area of chronic wounds, recurrence or dehiscence, i.e., the reappearance of the wound after complete wound closure, is recorded as an outcome and analysed as a rate at the end of the study. However, such an analysis does not include all patients randomized at the start of the study, but only those who have previously achieved complete wound closure. Since achieving complete wound closure is a process parameter, it cannot be assumed that the structural equality between the study arms achieved through randomization at the start of the study still exists in the patients included in the analysis. A randomized comparison is therefore not given, and no valid analysis can be performed in these constellations.

Alternatively, the sustainability of complete wound closure can be analysed. In order to assess the sustainability of complete wound closure, all randomized patients should be followed up for as long as possible, regardless of whether complete wound closure (possibly interim) has been achieved. This makes it possible to re-analyse the outcome of complete wound closure at a later point in time (after the primary time of analysis) and to use this to estimate the

sustainability of a previously observed effect on the outcome of complete wound closure. Further information on the duration of follow-up periods can be found in Section 5.1.4.

5.1.3.2.2 Partial wound closure – substantial improvement in the patients' life situation

Complete wound closure is usually the primary treatment goal, but in some situations, partial wound closure can also mean a substantial improvement in the patients' life situation.

Based solely on the advantage of one intervention over a control intervention in terms of reducing the size of a wound area, no benefit can be justified at first. For example, without knowledge and evaluation of the specific wound characteristics, it is unclear what a 50 percent reduction in wound area means for patients and whether this change is perceived as a noticeable improvement in their respective patient's life situation. In order to derive a benefit, it must therefore be sufficiently certain that partial wound closure has a direct impact on patient-relevant aspects. In particular, these include improvements in health-related quality of life, activities of daily living, pain, and a noticeable change in a stressful wound characteristics (e.g., ulceration) that goes beyond the size of the wound. To this end, the achievement of partial wound closure in clinical trials can be linked to the achievement of an improvement in at least one directly patient-relevant, temporally-associated outcome (examples below). This increases the likelihood that the partial wound closure observed under the intervention is relevant to the patient, as it is actually associated with an improvement in outcomes that are immediately noticeable to patients. Furthermore, linking partial wound closure to health-related quality of life or activities of daily living also takes into account potentially stressful aspects of wound care, such as the number of dressing changes.

Below are three examples of treatment situations and an appropriate outcome operationalization for each, which demonstrate a substantial improvement in the patients' life situation.

- Treatment situation: large (≥ 20 cm^2) surgical wound on the abdomen with no tendency to heal after 6 weeks
  - Outcome operationalization: Proportion of patients with a 75% reduction in wound area and simultaneous improvement in health-related quality of life as measured by the Short Form-36 Health Survey (SF-36) or the Short Form-12 Health Survey (SF-12) or another validated instrument for measuring health-related quality of life (response criterion 15% of the scale range)
- Treatment situation: large (≥ 10 cm^2) painful wound on the lower leg due to chronic venous insufficiency

  - Outcome operationalization: Proportion of patients with a 75% reduction in wound area and simultaneous improvement in the outcome of pain, measured, for example, using a VAS (response criterion 15% of the scale range).
- Treatment situation: multiple (≥ 5) ulcerated wounds of varying sizes caused by symptomatic metastatic basal cell carcinoma.
  - Outcome operationalization: Proportion of patients with a 50% reduction in wound area of all target lesions and simultaneous healing of all ulcerations without the occurrence of new lesions

In the situations described as examples, linking the outcome of wound area reduction with an outcome that is directly relevant to the patient sufficiently ensures that the outcome operationalizations used reflect a substantial improvement in the patients' life situation and that this improvement is also temporally associated with partial wound closure. These are therefore suitable for assessing treatment effects.

It should be noted that patients with chronic wounds sometimes have variable individual treatment goals. For example, some patients may focus on improving their activities of daily living (e.g., improving mobility), while others may be more concerned with reducing painful ulcerations. Against this background, individual goals and descriptions of the individual goal attainment levels can be useful in consultation between the patient and the medical staff, which can be operationalized in a study on Goal Attainment Scaling (GAS) (see below). The achievement of these individual treatment goals can also be linked to partial wound closure of, for example, 50% or 75% for the most debilitating wound(s).

Comments on the measurement method

It should be noted that there are currently no standardized measurement methods available for measuring wound area or reduction in wound area. According to the information in the S3 guideline ("Topical treatment for difficult-to-heal and/or chronic wounds due to PAD, diabetes mellitus, or chronic venous insufficiency"), this outcome is recorded by measuring with a ruler and then calculating using the perpendicular method (based on the longest length and widest width of a wound) [17]. Other methods are also mentioned, such as a measurement method based on digital images [17]. According to the information in the above-mentioned S3 guideline, systematic reviews of measuring instruments for diabetic foot ulcers conclude that the methods for measuring wound area have not yet been sufficiently investigated. However, measurement using a ruler and calculation according to the perpendicular method is named as a suitable method in this S3 guideline. The same method should always be used for wound area measurement within a study.

Another hurdle in recording the outcome arises from the fact that the speed of wound closure can vary during the healing process [5]. The result of this outcome is therefore dependent on

the previously defined time of analysis. It therefore makes sense to analyse data at several points in time and take them into account when assessing the effects of treatment.

Partial wound closure as a surrogate for complete wound closure

It is sometimes argued that a reduction in wound area is prognostic for achieving complete wound closure – partial wound closure is thus sometimes regarded as a prognostic marker for achieving complete wound closure [80-86]. However, there are currently no studies available that can be used to derive a valid threshold from which the achievement of complete wound closure can be predicted with sufficient certainty. Furthermore, a prognostic marker is not necessarily a valid surrogate for the outcome of interest (in this case: complete wound closure). Surrogate validation studies are necessary for this purpose. The current status of surrogate validation studies for the outcome of partial wound closure is presented in Section 5.2 .

5.1.3.2.3 Pain

Pain is a patient-relevant outcome. In patients with chronic wounds, pain is often a combination of chronic pain and acute pain (e.g., when changing wound dressings).

Instruments for recording pain

There are no objective measures for recording pain. Therefore, the outcome must be recorded as a patient-reported outcome. This should be done using a validated, indication-specific or generic instrument. An indication-specific instrument generally allows for more sensitive measurement of changes and is easier to interpret. It is therefore generally preferable to a generic instrument.

The exploratory search did not identify any validated indication-specific instruments for recording pain in patients with chronic wounds. Generic instruments are available that are based on simple scales such as a VAS, numerical rating scales (NRS), or Likert scales. Multidimensional instruments can also be used to record various aspects of pain. The validity of the instruments used in the studies must be proven in advance.

An example of a generic instrument for patient-reported measurement of pain intensity and impairment due to pain is the Brief Pain Inventory-Short Form (BPI-SF) [87]. Originally developed for patients with cancer, it is also suitable for measuring pain across indications and is widely used. The BPI-SF assesses pain intensity using four items: the most severe and least severe pain within the last 24 hours, average pain (without specifying the recall time), and current pain. The items are formulated as NRS with 11 levels each (0 = no pain to 10 = worst pain imaginable). The BPI-SF assesses the impairment caused by pain using 7 items with a recall period of 24 hours for: general activity, mood, walking ability, normal work, relations

with other people, sleep, and enjoyment of life. The items are also formulated as NRS with 11 levels (0 = no impairment to 10 = complete impairment).

Concomitant medication

In studies investigating the outcome of pain, there should be no restrictions on patients with regard to concomitant pain medication. It should also be ensured that pain medication can be adjusted to the individual patient at any time during the course of the study. The pain medication used in the study should correspond to the standard treatment used in everyday care. For the interpretation of the study results for the outcome of pain, it is also necessary to document all concomitant treatments throughout the entire study period. For the same reason, the pain medication intake prior to the start of the study and the response of the study population to pain medication should also be documented.

Timing of data collection

When recording the outcome of pain, the type of pain to be examined must be taken into account, e.g., intermittent or paroxysmal, essentially constant with varying degrees of intensity, or one-time. The EMA guideline on the clinical development of medicinal products for the treatment of pain [88] points out in this context that assessments must be adapted to the temporal course of the pain. The timing of recording the outcome “pain” should therefore be justified. Due to fluctuations in pain intensity throughout the day, assessment in the morning and evening of the same day is recommended for chronic pain. Furthermore, depending on the clinical situation, pain should not only be assessed when patients are at rest, but also during movement, in order to ensure a comprehensive assessment.

The use of patient diaries to document pain perception is recommended. The intervals between assessments should be sufficiently short to ensure reliable recording of pain intensity by affected patients.

5.1.3.2.4 Hospitalization

In studies on the treatment of chronic wounds, outcomes for both overall hospitalization and disease-related hospitalization – hospitalization due to chronic wounds – are recorded.

Hospitalization due to chronic wounds can be used as an operationalization to reflect severe disease-related events. To ensure that hospitalization is attributable to the chronic wound, events should be adjudicated adequately and transparently using a predefined list of wound-related complications (wound bleeding, wound infections, etc.). This allows potential differences in the healthcare context to be addressed in multinational studies.

5.1.3.2.5 Amputation

Patients with chronic wounds on the lower legs and feet (leg ulcer, diabetic foot ulcer) have an increased risk of amputation during the course of their illness. The occurrence of minor and major amputations is relevant to patients and should be recorded in clinical trials on chronic wounds of the extremities. Diagnostic methods for assessing the severity of circulatory disorders that are based solely on imaging or measurements, such as angiographic or Doppler sonographic findings or the ankle-brachial index, do not represent an operationalization of the outcome of amputation that alone can justify a benefit.

5.1.3.2.6 Wound infection

Microorganisms can be found in any type of wound. When microorganisms grow and multiply but do not cause any damage, this is referred to as colonization. Preventing colonization alone does not constitute a benefit, as microbiological findings or laboratory parameters (e.g., bacterial contamination) do not result in symptoms that are noticeable to patients. However, if microbial growth leads to cell damage and inflammation, this is referred to as a wound infection. A wound infection is usually noticeable to patients due to the classic signs of inflammation (redness, overheating, swelling, pain, and limited function) and can also lead to serious complications such as life-threatening sepsis in advanced stages. Wound infection is therefore a patient-relevant outcome.

The recording of the outcome of wound infection must be based on clinical signs and symptoms that are noticeable to patients. The recording of wound infections should be carried out using established systems for the respective wound entities. The Initiative for Chronic Wounds (ICW) has developed general criteria for the diagnosis of wound infection using the TILI score (Therapeutic Index for Local Infections) [20]. The detection of potentially pathogenic microorganisms, a surgically septic wound, or the presence of free pus indicates a direct need for treatment with antimicrobial therapy. In addition, the ICW classifies an infection as requiring treatment if at least 5 of the following non-specific criteria are present:

- Perilesional erythema
- Overheating
- Oedema, induration, and swelling
- Spontaneous pain or pressure pain
- Stagnation of wound healing
- Increase and/or change in the colour or odour of the exudate

Although the TILI score is primarily a diagnostic tool for determining the need for treatment, it is potentially possible to use it to record patient-relevant wound infections in clinical trials.

This is because the criteria mentioned (with the exception of the detection of potentially pathogenic microorganisms) can be directly perceived by the patient. However, it is important to document and report which of the criteria of the TILI score for determining wound infection in patients were met.

Timing of data collection

In studies on antimicrobial interventions, the type and presumed duration of the infection to be investigated must be taken into account when choosing the timing of the recording of the outcome "wound infection". Both the timing and the criteria for determining clinical cure must be predefined. A follow-up period is advisable, especially if the wound infection in question is known to have a high recurrence rate [89].

In studies investigating the occurrence of infections during wound treatment, the predefined data collection times should be selected at narrow intervals, depending on the known probability of infection. The choice of time periods should be justified in the study protocol.

5.1.3.2.7 Debridement and wound dressing changes

Outcomes relating to debridement or wound dressing changes are not outcomes that can alone justify a benefit, but should rather be seen as part of the treatment strategy. In studies on wound cleansing compresses, for example, both the number of debridements required and the time to complete debridement are recorded as outcomes. It is argued that debridement or wound dressing changes are often associated with pain for patients [47]. However, there is no scientific evidence that patients regularly experience increased pain with more frequent debridements under adequate pain therapy, regardless of the wound entity. In addition, pain can be recorded directly using patient-reported instruments (see section on the outcome of pain).

5.1.3.2.8 Restrictions on activities of daily living and social participation

Outcomes relating to activities of daily living and social participation are patient-relevant outcomes. However, such outcomes are rarely measured in clinical trials in the therapeutic area of chronic wound treatment.

The limitations experienced by affected patients in these two areas can result in particular from pain, limited mobility, and embarrassment due to wound odour/exudate [41].

Activities of daily living

Outcomes relating to activities of daily living are usually recorded by assessing a person's ability to perform basic and instrumental daily tasks independently [90,91]. Basic activities include bathing/showering, personal hygiene, dressing, using the toilet, and eating.

Instrumental activities include more complex activities that are necessary for independent living, such as preparing meals, shopping, or cleaning the house.

In the therapeutic area of chronic wounds, both basic and instrumental activities of daily living should be assessed using appropriate, validated instruments.

Social participation

There is no uniform, narrow definition of social participation in the literature. Various forms of social participation are described, including social bonds (relationships with people), informal social participation (joint activities with other people), and voluntary work [41,92].

Social participation and its subforms can be measured using validated instruments or subdomains of questionnaires on health-related quality of life.

Recording of the outcomes "activities of daily living" and "social participation" based on individualized goals

Goals for social participation or activities of daily living are difficult to define comprehensively for all patients. Patients with chronic wounds are very heterogeneous in their physical abilities and needs, so it may be useful to agree on individual goals for each patient. If no validated instruments are available to measure these outcomes, the GAS can be used to record and analyse them [93,94]. Individual goals and descriptions of the individual goal attainment levels are determined in consultation between the patient and the doctor. For each goal, the expected treatment success (level = 0) and the criteria for upward and downward deviations (much better = +2; better = +1; worse = −1; much worse = −2) are formulated in such a way that an independent observer is able to evaluate the result on this scale. The assessment is based on interviews with patients, which may also be recorded and presented to independent assessors. There is no maximum number of goals per patient; only one goal may be formulated [93].

Restrictions due to wound odour and wound exudate

The outcomes of wound odour and exudate (increase in the exudate volume and/or change in colour) are alone insufficient to justify a benefit based solely on direct measurement of the odour or exudate (e.g., using scales such as VAS or Likert scales or with a yes/no question). However, these events become relevant for patients when they lead to social isolation and limited participation in social life. These complex relationships cannot be reflected by simply asking about odour perception alone, for example. These outcomes must therefore always be assessed in relation to the resulting limitations on patients' activities of daily living or social participation.

5.1.3.2.9 Health state

Health state is a patient-relevant outcome. In studies on the treatment of chronic wounds, the EQ-5D questionnaire is often used as a tool for recording patient-reported outcomes.

The EQ-5D consists of 5 questions on various aspects of health to describe a health profile, a VAS to indicate health state (best imaginable health state – worst imaginable health state), and various tariffs that assign a value (utility value) between 1 (best possible health state) and 0 (death) or negative values (states worse than death) to the possible answer combinations in the first part (health profile).

Analyses of utility values can only be considered patient-relevant if the underlying tariff was generated on the basis of a patient population suitable for the respective question. If such an analysis is available, the outcome can be assigned to the outcome category of health-related quality of life. VAS analyses are also suitable. The outcome is referred to as health state and assigned to the outcome category of morbidity. In responder analyses for the VAS, a response criterion that reliably reflects a change noticeable to patients should be used (at least 15% of the scale range of the instrument).

5.1.3.2.10 Health-related quality of life

Outcomes for health-related quality of life are patient-relevant. In general, these should be recorded using a validated instrument. Only instruments that are suitable for use in clinical trials and have been validated accordingly should be used to record health-related quality of life.

There are both generic instruments and instruments specifically developed for use in patients with chronic wounds. Similar to the recommendation for recording pain (Section 5.1.3.2.3), an indication-specific instrument generally allows for a more sensitive measurement of changes and is easier to interpret. It is therefore generally preferable to a generic instrument.

One example of a generic, validated questionnaire for self-assessment of health-related quality of life is the SF-36. The questionnaire contains 36 items, but only 35 are used to calculate the SF-36 scores [95]. The questionnaire covers the following 8 domains: physical functioning (10 items), role physical (4 items), bodily pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role emotional (3 items), and mental health (5 items). A single score is calculated for each of the 8 domains. In addition, the 8 domains are combined into a score for the physical component (Physical Component Summary [PCS]) and a score for the mental component (Mental Component Summary [MCS]). The PCS and MCS are standardized using the US general population based on a mean of 50 and a standard deviation of 10 [95]. Higher scores indicate a better health-related quality of life. In addition to the SF-36, there is also a short form, the SF-12, which consists of 12 items that are also

included in the SF-36. The SF-12 covers the 8 domains of the SF-36 with 1 to 2 items. As part of the SF questionnaire system, the SF-12 is considered a valid generic instrument.

In the therapeutic area of chronic wounds, there are numerous indication-specific instruments that are used to record health-related quality of life. However, a substantial proportion of these instruments have shortcomings in terms of their development (e.g., lack of or unclear patient involvement) and validation, which is why they cannot be recommended primarily for recording health-related quality of life in studies. As part of an exploratory search, 11 indication-specific instruments for recording health-related quality of life in chronic wounds were identified. Publications on the development of the instruments were obtained from entries in the PROQOLID database [96] and, where applicable, systematic reviews from the COSMIN database [97]. In addition, information on the available language versions was obtained from the PROQOLID database. The available sources on the development of the instruments were reviewed in particular for information on the involvement of patients in the development process and information on validity, reliability, and sensitivity to change. For 2 of the 11 instruments (Ferrans and Powers Quality of Life Index – Wounds Version [FPQLI-WV][98] and Sheffield Preference-based Venous Ulcer-5D questionnaire [SPVU-5D] [99]), no assessment was possible because the questionnaire was not available in the identified literature and could not be identified via an additional exploratory search. For the Freiburg Life Quality Assessment – Wound Module [FLQA-w] [100], only the short version FLQA-wk could be identified via an additional exploratory search [101]. However, this short version contains one more item compared to the number of items described in the 2010 publication by Augustin [100] on the FLQA-w. It therefore remains unclear to what extent this short version is actually based on the FLQA-w. It was therefore not possible to assess the FLQA-w. A summary of the sources reviewed and the information they contain on the instrument can be found in Appendix B, Table 3 of the full rapid report.

The following are examples of the Wound-QoL and WOUND-Q instruments, which can be used in studies in the area of wound treatment to record health-related quality of life.

Wound-QoL

The Wound-QoL is a widely used questionnaire in the therapeutic area of chronic wound treatment. It was developed by Blome in 2014 [102] as a short questionnaire based on items from the FLQA-w [100], the Cardiff Wound Impact Schedule (CWIS) [103] and the Würzburg Wound Score (WWS) [104-106].

The Wound-QoL comprises 17 items on wound-related symptoms and the mental and functional effects of the wound. All items are 5-point Likert scales with the gradations "not at all," "a little," "moderately," "quite a lot," and "very much." The answers are coded in ascending order from 0 to 4 for analysis. An overall score is calculated as the average value of

all items. For this, at least 13 (75%) of all items must be answered. In addition, 3 subscales can be formed for physical aspects (body, items 1 to 5), psychological aspects (psyche, items 6 to 10), and activities of daily living (everyday life, items 11 to 16), also as the average of the items involved, with a maximum of one item missing in each case. Item 17 is not part of a subscale. The recall period is 7 days.

The publications reviewed on wound QoL do not indicate that patients were involved in the selection of items from the source questionnaire. In the scientific debate on the preliminary rapid report on 21 February 2025, one commenter described previously unpublished research results that address the lack of patient involvement. However, these were not made available to IQWiG by the time this final rapid report was completed.

WOUND-Q

The WOUND-Q is a validated instrument for measuring health-related quality of life in patients with various chronic and acute wound entities. The validation studies investigated diabetic foot ulcers, surgical wounds, pressure ulcers, venous and arterial ulcers, and infected wounds. The locations mainly included the lower extremities, but also the abdomen, chest, arms, and face.

The instrument comprises four domains with varying numbers of scales. The scales of the "Wound" and "HR-QoL" domains are relevant for measuring health-related quality of life. There is currently no validated German-language version of the WOUND-Q questionnaire (as of 03/2025).

Both the type of outcome recording and analysis must be specified in advance in the study protocol and documented accordingly. It can be specified that only certain scales are to be recorded.

5.1.3.2.11 Adverse effects

Adverse effects are usually recorded in studies in the form of adverse events (AEs). An AE is any adverse and unintended occurrence, symptom, or illness that is temporally associated with a medical intervention, for example, regardless of whether a causal relationship with the intervention is assumed or not [107].

In a clinical study on the treatment of chronic wounds, AEs that occurred during the course of the study should be documented according to an established system (e.g., Medical Dictionary for Regulatory Activities [MedDRA]), regardless of whether every AE is to be recorded or only a predefined selection based on content or severity. In any case, it is necessary to record all serious adverse events (SAEs) and all AEs that led to discontinuation of treatment. For these higher-level AE outcomes, the overall rates (patients with events) should be presented in each case.

Additional analyses of specific AEs and SAEs, for example at the level of system organ classes (SOCs) and preferred terms (PTs), can provide further information on AEs that are of particular relevance to the therapeutic area under investigation. For example, in studies on wound dressings, skin reactions and wound bleeding in the wound environment are potentially particularly relevant. Such AEs of particular importance, which are to be explicitly recorded and analysed in a study, must be predefined in the study protocol.

5.1.3.3 Combined outcomes in the therapeutic area of chronic wounds

In studies in the therapeutic area of chronic wounds, scores are sometimes used to record outcomes. One example is the Pressure Ulcer Scale for Healing (PUSH) score [108]. This score is composed of the components wound size, exudate volume, and tissue type (necrotic tissue, scab, granulation tissue, etc.).

Scores that are composed of different components are often analysed as composite outcomes. A composite outcome comprises at least two individual outcomes. In contrast to a paired outcome (see Section 5.1.3.2.2), the composite outcome is already reached when an event occurs in one component of this outcome. For a composite outcome to be considered patient-relevant, all individual components must be patient-relevant. In addition, results must be presented for all individual components. This is not the case, for example, with the PUSH score mentioned above, as none of the components are directly patient-relevant.

5.1.3.4 Appropriate analyses

Study results should be analysed according to the intention-to-treat (ITT) principle. This involves analysing all randomized patients according to their group allocation. To do this, missing values must be replaced in a suitable, predefined manner.

Various types of analysis (event rates, event time analyses, and continuous data [e.g., mean change over the course of the study]) are available for analysing study results. The choice of a suitable type of analysis depends on various factors. Depending on the indication, the treatment goal, the outcome recorded, the chosen operationalization, and the duration of the study, a decision must be made on the basis of content-related considerations as to whether the occurrence of an event, the time until the occurrence of an event, or a mean change at a specific point in time or over the entire course of the study is the appropriate type of analysis for answering the research question.

In any case, the planned outcome-related analyses must be predefined in a statistical analysis plan.

5.1.4 Key features for conducting studies in the area of chronic wounds

The following section describes specific aspects of the planning and conduct of clinical trials in the therapeutic area of chronic wounds. Explanations of general requirements, such as defining a suitable research question or developing a study protocol before enrolling patients, are not provided. It should be noted that, as a rule, all studies should be registered in a study registry accredited by the World Health Organization (e.g., on ClinicalTrials.gov) and the study protocol should be made publicly available there.

5.1.4.1 Randomization

RCTs can be used to demonstrate causality. RCTs are also feasible in the therapeutic area of chronic wound treatment and represent the standard study design.

In randomization, patients are randomly assigned to study arms. This prevents bias due to confounding (or selection bias) – not only with regard to known influencing factors, but also with regard to unknown ones (to maintain structural equality). The aim is to ensure that differences between the groups (e.g., in terms of patient characteristics and/or wound characteristics) that are detected at the end of a study are actually caused by the interventions. Adequate randomization depends on two factors: first, an unpredictable, random randomization sequence and, second, the concealment of this sequence until the final allocation, known as allocation concealment. Randomized studies are also possible as routine practice studies without major restrictions on inclusion criteria and with low-resource data collection, e.g., as registry-based RCTs [109].

Randomization of patients vs. randomization of wounds

In studies on wound treatment, either the patients or the individual wounds can be randomized. As a rule, randomization of patients is appropriate. In this case, only one wound per patient should be considered. Randomization of wounds (inclusion of several wounds per patient) is only appropriate in very specific constellations, depending on the intervention and the treatment goal. For example, the study interventions may only have a local effect and not a systemic one, and the treatment goal must be locally measurable. Randomization of wounds would be possible in a study with the goal of complete wound closure when comparing two locally effective interventions, for example, but not when the treatment goal is pain reduction. It should be noted that when analysing multiple wounds in a patient, appropriate statistical analyses must be determined for an adequate analysis of the results due to the dependency of the data collected.

Stratification

In studies with a small sample size, randomization may still result in imbalances between the study arms in terms of certain characteristics (of the patients or wounds). To avoid any resulting bias, randomization should be stratified (according to patient or wound

characteristics). Chronic wounds, even those of the same entity, can exhibit substantial heterogeneity. In such cases, in order to maintain structural equality between the study arms, suitable stratification factors should be selected for randomization, such as severity, wound size, wound location, or time since the wound appeared. If patients with chronic wounds of different entities are included, randomization should be stratified according to these entities (see also Section 5.1.2).

5.1.4.2 Adaptive study design

RCTs with an adaptive design are also conceivable for answering questions in the therapeutic area of wound treatment. Adaptive designs are particularly useful when study planning (e.g., sample size calculation) is difficult due to limited knowledge about the possible course of the study (e.g., anticipated dropout rates, number of expected events). Such designs make it possible to respond to interim findings obtained during the study and to make adjustments for the further course of the study. In such a design, the study is divided into two or more consecutive sub-studies, the results of which are independent of each other. After each substudy, interim analyses are performed and it is checked whether the criteria previously defined in a study protocol have been met and whether the following substudies can be continued, need to be adjusted (e.g., increase or reduction in the sample size) [110], or whether the entire study should be terminated. For example, the study protocol for an RCT may specify that an interim analysis for the outcome of complete wound closure will be performed after 50% of the planned sample size has been recruited. If the effects are smaller than expected in the interim analysis, the sample size for the further course of the study can be increased. If the effect is substantially greater than expected, the sample size can be reduced or, if necessary, the study can be terminated prematurely.

The advantages are that these studies potentially deliver results more quickly through early interim analyses and that the number of patients to be included can be reduced if the results are clearly positive or negative [111]. However, such designs are challenging due to their greater complexity, and interpreting the results is potentially more difficult [111]. In order to adequately conduct a study with an adaptive design and report its results, guidelines such as the extension to the Consolidated Standards of Reporting Trials (CONSORT) statement on studies with adaptive designs [112] should be followed.

5.1.4.3 Blinding

In general, a lack of blinding of study participants, doctors, and outcome assessors leads to potentially biased results in clinical trials. For this reason, blinding should always be used for these groups of people in studies whenever possible in order to avoid possible bias in the study results due to knowledge of group allocation. Blinding must be maintained until the end of the study.

In unblinded studies on wound treatment, it is often stated that blinding is not possible without giving specific reasons. This is discussed, among other places, in the 2010 publication by Buchberger [7] on the importance of growth factors for the treatment of chronic wounds. It describes that in the studies considered, either no reasons or no convincing reasons are given for the lack of blinding, blinding is not mentioned despite being a practicable option, or blinding of at least the outcome assessors is not considered. Blinding study participants, doctors, and outcome assessors in studies on chronic wounds can be challenging, but in most cases, it is fundamentally possible (see following sections). If blinding is not carried out, it should at least be ensured that the mandatory participant information and education about the potential benefits or harms of the treatment options used in the study is provided in a neutral manner. For example, it should be avoided that the new intervention is described by the informing doctor as superior to the control intervention, in order to minimize bias due to knowledge of treatment allocation.

Blinding of patients

Patients may (unconsciously) influence their response to the intervention if they know which group they belong to. For example, they may assume that a novel treatment is more effective than the control treatment, which is, for example, the standard treatment [60]. This can lead to patients who know that they are receiving a novel treatment overestimating its effect. Conversely, patients may also be critical of the novel treatment, which can lead to an underestimated effect. In addition, knowledge of group allocation can affect compliance and lead to increased study dropout rates in the study arm with the novel treatment or in the control arm.

In studies in the therapeutic area of chronic wounds, blinding patients can be challenging due to potentially visible differences between the interventions. However, it can generally be assumed that there are usually ways to achieve adequate blinding. For example, when comparing wound dressings, they can be covered with an identical secondary dressing. Appropriate options with the aim of ensuring adequate blinding of patients must be considered during study planning, depending on the nature of the intervention used. When changing wound dressings, blinding can be maintained by using a screen for patients, depending on the location of the wound.

Blinding of study staff

Study staff such as doctors should also be blinded to prevent unconscious influence on treatment. It is conceivable that, depending on their attitude toward the test intervention, study doctors may provide different levels of care to patients depending on their group allocation and, for example, administer adjunctive treatments to varying degrees [60]. They may also be more likely to advise patients to discontinue the study or discourage them from doing so if they are aware of their group allocation.

The challenges involved in blinding study staff are similar to those involved in blinding patients. However, adequate blinding is feasible in most study settings. For example, the dressing can be opened by a qualified person other than the responsible medical staff and reapplied after the ward round.

If such blinding is not carried out, it must be ensured that local wound treatment is used appropriately and fairly in a study. The treatment algorithm, in particular surgical treatment or systemic antibiotic treatment, should be clearly specified. All treatments should be fully documented.

The possible procedures for achieving blinding should be determined during study planning.

Blinding of outcome assessors

Knowledge of group allocation may lead outcome assessors to evaluate outcomes differently in the study group receiving a novel treatment than in the other study group due to a presumed superiority of this treatment [60]. Outcome assessment should therefore always be blinded to ensure an objective, unbiased evaluation of the results. Even if there are situations where it is not possible to blind patients and/or study staff for understandable reasons, it is almost always possible to have the results of a study recorded by someone who is independent and blinded to the intervention. For example, when comparing dressings with hydrogels of different colours, the dressing can be removed by another person, who does not need to be blinded, before an infection is assessed. The assessment could then be carried out blinded. Another option is the assessment of outcomes such as wound healing based on photographic documentation by a blinded, central, and independent committee.

Importance and challenges of blinding

The importance of blinding depends, among other things, on the type of outcome. For example, the results of the outcome for mortality are less susceptible to potential bias if the patients and study staff are not blinded, because this outcome can be assessed objectively even without blinding. The situation is different, for example, with the outcome of pain. This is based on the subjective feelings of patients, which can be strongly influenced by psychological factors. If patients are aware of their treatment, this can influence their expectations of pain and, as a result, their perception of pain, leading to potentially biased results. Accordingly, comprehensive blinding is more important in studies with the treatment goal of improving chronic pain than in studies on complete wound closure, for example.

However, situations are conceivable in which the measures used solely to maintain blinding in a study, e.g., the transferability of the results to the relevant healthcare context, are jeopardized. For example, blinding measures may lead to additional, medically unnecessary dressing changes or hospital visits when different treatment strategies are used for the test and control interventions. This can result in noticeable restrictions in health-related quality of

life that would not have occurred in everyday care. The effects observed in the study are therefore potentially no longer transferable to the healthcare context. In such cases, the advantages and disadvantages of blinding must be weighed up. The decision for or against blinding measures when conducting a study should be documented and justified in the study protocol.

5.1.4.4 Patient population

When defining the inclusion and exclusion criteria, care should be taken not to restrict the patient population specified in the research question to such an extent that relevant patient groups from everyday care are excluded from participation. Patients with chronic wounds are often older and frequently suffer from comorbidities (e.g., renal insufficiency, heart failure, immobility). In addition, the wounds of patients in everyday care present in different conditions. Excluding patients above a certain age limit, with certain comorbidities or degrees of chronic wound severity, therefore potentially substantially limits the transferability of the results to the healthcare context and should be avoided.

As explained in Section 5.1.2, there are various entities of chronic wounds. These differ in terms of the cause of the wound, the underlying diseases, the treatment recommendations, and the respective wound healing prognosis.

The patients included in the study must represent the patient population of interest for the research question. Depending on the research question, it may be appropriate to include, for example, several wound entities in one study, or wounds with different characteristics such as wound condition, size, depth, and location, or the presence of infection. If different wound entities or wounds with different relevant characteristics are included in one study, it is necessary to define these as stratification factors and plan appropriate subgroup analyses. The sample size should be planned in such a way that meaningful results can be generated for the overall population. The frequencies of the individual wound entities should be taken into account (see Section 5.1.2.1). The sample size determined should also allow for the identification of possible interactions between subgroups (e.g., wound entity or wound characteristics) and the intervention.

Due to these different factors, it is essential in the context of study planning to determine which characteristics of the population and/or chronic wounds, in addition to the intervention under investigation, could influence the respective study outcomes, and to take these into account in the context of stratified randomization when assigning patients to groups or in the context of subgroup analyses [39,67].

5.1.4.5 Intervention, control treatments, and concomitant treatments

A necessary prerequisite for meaningful studies is that the respective treatments in the study arms are clearly defined in the study protocol and, as far as possible, differ between the study arms only in the test or control intervention. The respective instructions for use of the interventions employed must be taken into account. The control treatment in a study should reflect the standard treatment for the treatment stage of the respective chronic wound according to the current state of scientific knowledge and include all possibilities of wound treatment – with the exception of the test intervention.

When planning the study, it should be noted that wound treatment during the study may in most cases consist of a combination of different wound type- and phase-specific interventions or treatment breaks. It may therefore be necessary in both study arms to change wound products or forms of treatment as required during the course of the study or to take treatment breaks in line with the treatment strategy. This means that the test interventions, as part of a treatment strategy, are often only used for a short period of time (e.g., only in a specific phase of wound healing) [19]. The study protocol should therefore specify as precisely as possible the treatment algorithm for the controlled continuation of treatment after the initial study treatment. Accordingly, pathways for optimal treatment management should be defined that, in addition to the test and control interventions, ensure largely standardized and phase-appropriate treatment of all included patients after the initial study treatment. The treatment algorithm and the indication for a certain treatment should be monitored and documented within the study, and the study staff must be trained accordingly. To ensure that a treatment strategy is followed in as standardized a manner as possible, a blinded independent committee can be appointed to make the relevant treatment recommendations, taking into account the protocol specifications.

Concomitant treatments for the wound (e.g., pressure relief measures, pain medication) and for the underlying diseases causing chronic wounds (e.g., diabetes mellitus, chronic venous insufficiency, etc.) should also be applied equally in the study arms and correspond to current standard care. The concomitant treatments permitted in the study and the criteria for their use should be specified in the study protocol.

5.1.4.6 Study duration

In order to obtain meaningful results, a sufficiently long treatment period – in accordance with the respective instructions for use, if applicable – and a sufficiently long follow-up period for the outcomes recorded are required. The minimum duration of a clinical study (total study duration) in the therapeutic area of chronic wounds is variable and depends on the treatment goal and the outcomes considered. The following information serves as a basic guide; deviating total study durations are also conceivable if justified.

In studies with the treatment goal of healing (complete wound closure), the duration should be based on the expected time to sustainable healing. With this treatment goal, the total study duration is therefore determined by the time to expected complete wound closure plus follow-up to ensure sustainability. A minimum total study duration of 6 months is assumed for this purpose. However, studies on large wounds with an expected poor prognosis for healing may require a substantially longer duration. In line with FDA recommendations [26], the sustainability of complete wound closure should be assessed 3 months after the initial assessment of this outcome by reassessing complete wound closure. In studies with the treatment goal of substantial improvement (partial wound closure coupled with an outcome directly relevant to the patient), shorter overall study durations may be sufficient, but should not be less than 3 months.

However, there are also patient-relevant outcomes in this therapeutic area where a substantial improvement for a patient can be achieved or observed in a shorter period of time. For example, unlike with chronic pain, an observation period of 14 days may be appropriate for assessing the reduction of acute pain. Exceptions to this must be justified (e.g., in the case of a substantially shorter treatment duration with one wound product). When investigating interventions with short-term treatment goals (such as infection resolution or pain reduction), however, the overarching goal for the use of wound treatment products must be considered, namely to contribute to complete wound healing or at least to achieve a substantial improvement in the patient's life situation. It is therefore not reasonable to derive the benefit of a test intervention for wound treatment solely on the basis of the short-term effect observed or to plan studies with a shortened study duration of less than 3 months. It cannot be ruled out that phase-specific interventions that are only used for a short period of time and whose benefits are to be justified by short-term outcomes may have an influence on outcomes that can only be achieved later, such as complete wound closure. For example, it is conceivable that a novel antiseptic may achieve infection resolution more quickly than the control treatment, but ultimately have a negative effect on complete wound closure. It should be noted that differences in outcomes that are only achievable at a later stage in a randomized study can also be attributed to the initial study treatment if further treatment options were used during the course of the study. To this end, it is important that patients in an RCT receive treatment defined according to standardized uniform criteria in all treatment arms, even in later phases of wound healing (see also Section 5.1.4.5).

5.1.4.7 Transferability of study results between wound entities or interventions

When considering the issue of transferability of study results from one wound entity to other wound entities, it should be noted that chronic wounds often occur as a result of various underlying diseases with distinct pathophysiology (see Section 5.1.2), which must also be treated when treating the chronic wound. Not only do wound management and/or the intervention being tested influence the healing process, but also the presence of a possible

underlying disease and the success of the concomitant treatment used for the underlying disease [19,39]. This substantially limits the possibility of transferring study results, regardless of the evidence that may exist. For example, Jull 2015 [40] points out that in the case of chronic wounds such as pressure ulcers and diabetic foot ulcers, the management of the underlying health problem may have a greater influence on the healing process than honey therapy for the treatment of chronic wounds examined in this review. The transferability of study results from one wound entity to another cannot be assumed as a matter of principle.

In justified cases, the transferability of study results (e.g., from one type of wound to another; from one intervention to another) can be examined and, if appropriate, implemented.

The methodological approach to assessing the transferability of evidence consists of using the evidence to demonstrate, on the basis of a partially modified question (e.g., different intervention; different population), that there is sufficient similarity in the effects relevant to benefits and harms. To this end, certain minimum criteria must be met with regard to the processing of the available evidence. First, the reference and target questions must be defined. This must be followed by systematic information retrieval to ensure the completeness of the study pool for both the reference and target questions. In any case, it is essential that the specific characteristics of the patients and the chronic wounds are comprehensively processed for the study reports and publications relevant to the transfer (both for the reference and target questions) [39].

The transfer of evidence is fundamentally subject to a high degree of uncertainty. Therefore, studies designed to answer the reference question should demonstrate sufficiently large and consistent effects across multiple outcomes.

5.2 Surrogate validation studies on the outcome of partial wound closure

For this report, an evaluation of surrogate validation studies on the outcome of partial wound closure was carried out in accordance with the commission and with the General Methods of the Institute [1]. This section first presents the results of the information retrieval for surrogate validation studies on the outcome of partial wound closure. This is followed by a definition of surrogate outcomes and their use in Section 5.2.3.1. Section 5.2.3.2 describes and methodically classifies the current data available for the validation of partial wound closure as a surrogate based on the information retrieved. Section 5.2.3.3 sets out the general methodological principles for surrogate validation. Finally, Section 5.2.3.4 explains, by way of example, the specific procedure for conducting a surrogate validation study on the outcome of partial wound closure in the therapeutic area of chronic wounds.

5.2.1 Focused information retrieval

5.2.1.1 Bibliographic databases

Figure 1 shows the results of the systematic literature search for relevant surrogate validation studies in the bibliographic databases according to the criteria for study inclusion. The search strategies for searching bibliographic databases can be found in Section A.2 of the full report. The last search took place on 19 June 2024.

The references of the hits that were reviewed in full text but excluded can be found in Section A1 of the full report.

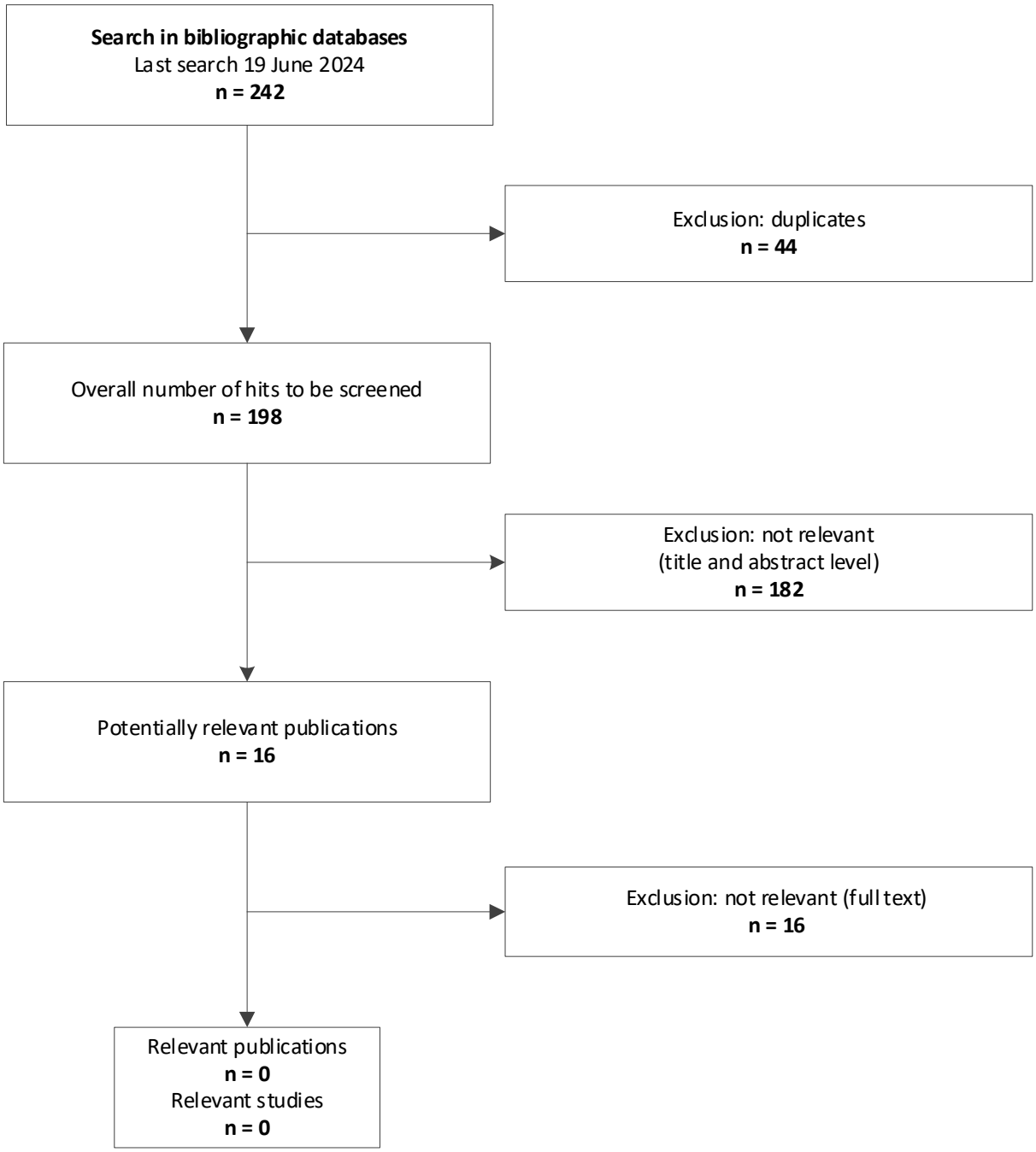

Figure 1: Results of the focused information retrieval from the bibliographic databases and the study selection for surrogate validations

5.2.1.2 Additional sources of information and search techniques

As part of the information retrieval process, the websites of the G-BA, IQWiG, the FDA, and the EMA (see Section A.2.2 of the full report) were searched.

No relevant studies or documents were found that had not already been identified through other search steps.

5.2.2 Resulting study pool

No relevant studies were identified through the focused information retrieval process. There are therefore no suitable studies available for surrogate validation of the outcome of partial wound closure, regardless of its definition for the outcome of complete wound closure.

5.2.3 Current evidence base and possible approach to surrogate validation of partial wound closure as a surrogate for patient-relevant outcomes

5.2.3.1 Definition and use of a surrogate outcome

In general, a surrogate outcome is an outcome that is used instead of the patient-relevant outcome of interest in order to obtain conclusions earlier and more easily [113]. The reason for this is that measuring the actual patient-relevant outcome is too difficult or it occurs only rarely or very late. The surrogate outcome can then be used to derive conclusions about the effect on the actual outcome of interest based on the observed effect on the surrogate outcome. IQWiG's rapid report A10-05 [114] describes the methodological principles for surrogate validation. General information on the use of surrogates can be found, for example, in the CONSORT/Standard Protocol Items: Recommendations for Interventional Trials [SPIRIT] Statement Extension for Surrogates [115,116] and for the validation of surrogate outcomes using meta-analysis in a publication by Xie 2019 [117].

5.2.3.2 Current evidence base on the validation of partial wound closure as a surrogate

The systematic search for suitable studies investigating the validity of the outcome of partial wound closure as a surrogate for patient-relevant outcomes did not yield any studies that met the requirements (see Section 5.2.2) for a surrogate validation study. In most of the studies reviewed in full text, the aim was to analyse the relationship between partial wound closure and complete wound closure, but in most of the studies reviewed (with the exception of Gwilym 2023 [118]), no systematic information retrieval was carried out. An adequate evidence base for surrogate validation was therefore not guaranteed.

The publication identified in the search (Gwilym 2023 [118]) is discussed below as an example. Although this review does not meet the methodological requirements for a surrogate validation study, it was one of the few studies that most closely addressed the issue of surrogate validation for partial wound closure. The following section highlights the areas in which this review does not meet the requirements.

The aim of the Gwilym 2023 [118] analysis was to summarize all available evidence for the evaluation of the outcome of partial wound closure as a predictor of complete wound closure in diabetic foot and venous leg ulcers and to determine the relevance of this outcome. Studies that examined patients with diabetic foot ulcers or venous leg ulcers were included. There were no restrictions on the type and design of the studies to be considered. In addition to

comparative cohort studies, the study pool also includes non-comparative cohort studies and only one RCT.

In order to obtain a suitable study pool, only RCTs in which both partial wound closure and complete wound closure were recorded and the respective treatment effects were reported should have been considered, as causal treatment effects can generally only be derived with sufficient certainty from RCTs and, in addition, an estimate (with a low risk of bias) of the size of the treatment effects is required for a surrogate validation study. Based on only one RCT, as in Gwilym 2023 [118], it is not possible to verify validity using adequate correlation-based methods.

Subsequently, Gwilym 2023 [118] compared the extent to which the results for partial wound closure corresponded to the results for complete wound closure (sensitivity, specificity, positive predictive value, negative predictive value). The aim was to examine whether partial wound closure is a good predictor of complete wound closure. However, this type of analysis does not allow the correlation of treatment effects between the surrogate outcome and the outcome of interest to be determined. In order to use partial wound closure as a surrogate for complete wound closure, there must be a sufficiently high correlation between the effects of an intervention on partial wound closure and the effects of this intervention on complete wound closure [1,114,119,120]. This means that a change in the effect for the outcome of partial wound closure is accompanied by a change in the effect for the outcome of complete wound closure that is in the same direction and quantitatively sufficiently similar [1,114,119,120]. After validation, it should be possible to use the results from the surrogate validation to draw conclusions about the (uninvestigated) effect of complete wound closure for studies in which only the effect of partial wound closure is reported. This is not possible based on the available analysis by Gwilym 2023.

Due to the aspects mentioned above, based on the review by Gwilym 2023 [118], no conclusion can be drawn about the validity of partial wound closure as a surrogate for complete wound closure.

5.2.3.3 General options for surrogate validation

Based on the available results/data/studies, it is not possible to draw a general conclusion as to whether partial wound closure is fundamentally a suitable and valid surrogate for another patient-relevant outcome for patients with chronic wounds.

As a general rule, surrogate outcomes should only be considered if they have been validated in a complete study pool using appropriate statistical methods [1]. This validation should be described in detail [117]. In addition, there are special situations in which validity can be recognized even without a validation study.

Assessment of validity based on a surrogate validation study

For an assessment using a surrogate validation study, it must be predefined whether a specific validation, i.e., the relationship for a specific combination of indication, intervention, and outcome definition, should be considered, or whether a comprehensive validation, i.e., across different indications, interventions, and/or different outcome operationalizations, should be performed. Furthermore, the following criteria should be met:

- In the case of a specific validation, all studies considered have the predefined indication, intervention, and outcome definitions.
- In the case of a comprehensive validation, the relationship between the surrogate outcome and the outcome of interest is consistent for any subset of studies or restrictions to specific indication or intervention areas.

Once these criteria have been specified, a systematic search for RCTs meeting these criteria must be conducted. Only studies of sufficiently high quality (in terms of RCTs) that have recorded and reported the surrogate outcome and the outcome of interest in the relevant population may be included. The study pool must be complete. In the case of a specific validation, this means that all studies that have been conducted in this population for the specified indication with the specified interventions and the recorded outcomes must be included. In the case of a comprehensive validation, studies with all indications and interventions of interest in the population that have recorded and reported the surrogate outcome and the outcome of interest should be included if possible. The studies identified for the validation must be taken into account in their entirety. Ideally, these studies also report individual patient data. This allows to take into account both the correlation within the studies and between the studies [121].

If the study pool has been created using a systematic search and can be assumed to be complete, the correlation is estimated using methodologically recognized validation procedures. The correlation must be robust for the comprehensive validation, i.e., it must also deliver consistent results in sensitivity analyses, e.g., for subgroups.

Recognized validation methods are correlation-based methods (see rapid report A10-05 [114]), such as the consideration of the correlation between the effects at the study level and the surrogate threshold effect (STE) [119,120]. The STE can be calculated to test whether an effect on the surrogate indicates an effect on the outcome of interest in a new study. It represents the lower threshold above which an effect on the surrogate must fully lie in order to infer an effect on the outcome of interest. The results on the STE are generally preferred to the results on the correlation. The thresholds for the correlation and for the assessment of the STE, as well as the algorithm for determining validity and the consequences thereof, are based on the information provided in the rapid report for commission A10-05 [114].

Assessment of validity in the absence of a surrogate validation study

In addition, there are special situations in which validity can be recognized even without a surrogate validation study as described above. For this, it is necessary that the relationship between the patient-relevant outcome and the surrogate outcome is biologically/medically clearly plausible and that one of the following criteria is met:

1) The occurrence of the surrogate outcome leads to a dramatically reduced risk (point estimate factor 1/10 or smaller) with regard to the actual outcome.
2) The occurrence of the surrogate outcome leads to a substantially reduced risk (point estimate factor 1/5 or smaller) with regard to the actual outcome. In addition, the risk with regard to the actual outcome reaches a minimal level, e.g., that of a non-diseased population.
3) The occurrence of the surrogate outcome immediately and inevitably also means the occurrence of the actual outcome.

For Cases 1 and 2, additional conditions must be met. For example, statistically significant results must be available, at least from cohort studies relating to patients undergoing treatment; data on the natural course of the disease are not sufficient. Close specificity of intervention and indication is not required. In addition, the follow-up period must be sufficiently long to accurately assess the risk of the actual outcome occurring. Furthermore, at least a focused search should have been conducted to obtain the evidence base.

An example of Case 2 is the surrogate outcome of sustained viral response (SVR) for the patient-relevant outcome of hepatocellular carcinoma (HCC) in the indication of hepatitis C (treatment-naive or treatment-experienced, without cirrhosis for various genotypes). The risk of HCC occurring under SVR is substantially lower than without SVR, with a relative risk (RR) of 0.21. In addition, the risk of HCC under SVR is comparable to the risk of HCC in the non-diseased population [122].

Examples of Case 3 are the surrogate outcome of virological response for the patient-relevant outcome of acquired immunodeficiency syndrome (AIDS)-related disease/death in patients with untreated human immunodeficiency virus (HIV) infections with virus type 1, and the surrogate outcome of severe acidosis for the patient-relevant outcome of immediate severe impairment in newborns with heart defects [123].

5.2.3.4 Specific approach for validating partial wound closure as a surrogate

The following section describes an example of the specific planning of a comprehensive surrogate validation of the outcome of partial wound closure for the outcome of complete wound closure. This can also be carried out analogously for other meaningful, patient-relevant outcomes. Such a research plan should be documented in as much detail as possible in a

protocol and published prior to implementation [117]. Specifications must be made for the research question, such as the population under consideration and the surrogate outcome to be validated, as well as the patient-relevant outcome of interest and the methodology of the search and analysis. Due to the very broad approach of comprehensive validation, further considerations regarding specific subgroup and sensitivity analyses, e.g., for different entities, indications, or interventions, must be made in advance.

Inclusion criteria for surrogate validation for partial wound closure

First, the inclusion and exclusion criteria are defined, taking into account the principles for information retrieval described in Section 5.2.3.3.

Indication

Patients with chronic wounds.

Intervention – comparison

No restrictions on intervention or comparison.

Outcomes

- Surrogate outcome: percentage reduction in wound area:

  For the surrogate outcome, it should be specified in advance how different percentage reductions in wound area will be handled. For example, classification into categories such as < 20%, 20% to 40%, 40% to 60%, 60% to 80%, > 80% would be possible.

- Outcome of interest: complete wound closure

- Study duration:

  The minimum study duration is 6 months due to the achievement of the outcome of complete wound closure (see Section 5.1.4). However, depending on the patient-relevant outcome of interest, a different study duration may be appropriate (see Section 5.1.4).

Study type

RCT

Information retrieval

To ensure the completeness of the study pool, systematic information retrieval using appropriate search strategies is necessary. The completeness of the study pool is particularly challenging in the area of medical devices, as there is no general registration requirement for such studies. Therefore, manufacturer inquiries are generally useful in order to achieve completeness of the study pool.

Primary sources of information

- Bibliographic databases
- Study registries
- Manufacturer inquiries
  - Manufacturers of interventions relevant to surrogate validation are identified through an exploratory search. Specifying the inclusion and exclusion criteria listed above, they are asked to identify relevant studies they conducted for the present research question and to submit the corresponding study data in the form of study reports. This applies in particular to studies that have not yet been published. The additional submission of individual patient data is desirable.

Statistical analysis

If the conditions for the study pool are met, the correlation is estimated using methodologically recognized validation procedures. Recognized validation procedures are correlation-based procedures (see rapid report A10-05 [114]) such as the consideration of the correlation between the effects at the study level and the STE [119,120]. The thresholds for the correlation and for the assessment of the STE, as well as the algorithm for determining validity and the consequences thereof, should be based on the information provided in the rapid report on commission A10-05 [114].

Subgroup and sensitivity analyses

In the area of chronic wounds, it can be assumed that the validity of a surrogate cannot be transferred to the majority of wounds, or only to a limited extent (see Section 5.1.2). For the comprehensive validation of partial wound closure as a surrogate for other patient-relevant outcomes, it therefore makes sense to define certain subgroups in advance, such as wound entities, categorical degree of partial wound closure, wound size, comorbidities, etc., for which validity is to be tested. Any heterogeneity in the effects should be adequately explained and taken into account. In the case of unexplained heterogeneity, further divisions of the study pool can be made in the form of sensitivity analyses, provided this is reasonably possible given the size of the study pool. In principle, the correlation should be consistent for any subsets of studies or when restricted to specific indication or intervention areas. This serves to test the robustness of the correlation. Additional methods such as cross-validation, bootstrap validation, or leave-one-out validation [117] can be used to test how the inclusion or exclusion of studies affects the validation result.

Derivation of conclusions about the surrogate of partial wound closure

Based on the example of surrogate validation described here, conclusions can be drawn about the validity of partial wound closure as a surrogate for complete wound closure after the analyses have been completed. As described above, in addition to testing for validity in the

overall pool, a comprehensive surrogate validation should examine whether and for which prespecified subgroups or subsets the validity of the surrogate could be demonstrated. If necessary, the examination of the overall pool may reveal additional subgroups that should also be considered. The results for individual subgroups or subsets may potentially show that the surrogate is not equally valid for all subgroups or subsets.

6 Discussion

Based on health insurance data, it has been determined that approximately 800,000 people in Germany are affected by chronic wounds [34,42]. The patients affected live with substantial and long-term limitations. The treatment of chronic wounds is complex and there are numerous treatment options available. However, there is a lack of meaningful clinical trials and evidence-based treatment recommendations based on them. Large parts of this therapeutic area remain unexplored.

The lack of high-quality evidence makes rational treatment and reimbursement decisions difficult or even impossible. Improving the evidence base is therefore essential for the care of patients with chronic wounds [124]. Overall, it is clear that the basic requirements for clinical trials on wound products hardly differ from the requirements for clinical trials on other medical interventions – the same applies to the framework conditions. Therefore, any demands for substantially different (mostly lower) evidence requirements for wound products are medically and scientifically unfounded and not in the interest of good patient care.

This scientific report identified key aspects in the conduct of studies in the therapeutic area of wound treatment that offer starting points for improving the conduct and reporting of valid and meaningful studies in the future.

Regulatory requirements for wound care products

Wound care products are generally subject to the German Medical Devices Act, which means that manufacturers only have to demonstrate technical safety within the framework of CE marking and prove the clinical performance and acceptability of the risk-benefit ratio of their products [125]. If the dressings meet the definition of the German Drug Directive, they can be prescribed to patients at the expense of the statutory health insurance system.

The demonstration of benefit based on high-quality evidence is currently only required for medical devices that belong to a high-risk class. This is reflected in the available evidence base in the therapeutic area of chronic wounds, which do not belong to medical devices with a high-risk class. For example, the S3 guideline on topical treatment for difficult-to-heal and/or chronic wounds due to PAD, diabetes mellitus, or chronic venous insufficiency [17] provides a total of 53 recommendations for the diagnosis and treatment of chronic wounds, but only 14 of these recommendations are based on evidence (defined as based on study results). Thirty-nine recommendations are based exclusively on expert opinions (consensus-based). There is a need for action here to improve the evidence base for rational treatment decisions in the interests of patients.

Against this background, it seems sensible that, at least for wound dressings that actively influence the physiological and pathophysiological processes of wound healing through

pharmacological, immunological, or metabolic properties, a new legal regulation has been created that requires a demonstration of benefit for these very products. In future, these products, known as "other wound treatment products" ("Sonstige Produkte zur Wundbehandlung", sPzW), can only be included in Annex V of the German Drug Directive [126] and thus become prescribable if their benefit has been demonstrated. This represents an important incentive to improve evidence generation in the therapeutic area of chronic wounds and is therefore to be welcomed in principle [19]. It should also be emphasized here that the G-BA is offering manufacturers consultation services to support both study planning and data analysis. This central consultation service is expected to result in a better evidence base for these products in the future, thus enabling evidence-based care.

Improving study planning and conduct

Reviews of various interventions in the therapeutic area of chronic wound treatment describe substantial methodological shortcomings in the identified studies with regard to study design, conduct, and analysis [5,9,46,50,58,59]. These include the formulation of adequate research questions, the definition and recording of relevant outcomes, comprehensible sample size calculation, and blinding. Studies with such fundamental shortcomings are not economically viable in terms of research and ultimately do not provide any relevant insights for patient care.

In the area of drug approval, a large number of uniform guidelines with recommendations (ICH guidelines) have been developed and implemented in recent decades within the framework of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), covering topics such as quality and safety as well as preclinical/clinical requirements. These guidelines can serve as a guide and can also be used for the testing of wound treatment product; it would be desirable to establish and implement such standards for the development of these products.

Publication of clinical trials

In addition to the lack of planning and conduct of high-quality RCTs in the therapeutic area of chronic wound treatment, the results of the studies that have been conducted are often not published at all or are often not published in full [36,37]. This is also due to the fact that there is no registration requirement for studies in the therapeutic area of wound treatment or for studies on medical devices in general – this potentially results in publication bias. On the one hand, this is problematic because patients and doctors do not have access to potentially relevant results for treatment decisions. On the other hand, existing limited resources are potentially used to answer questions in clinical trials, even though these results already exist but have not been published. Furthermore, secondary research projects (e.g., surrogate validations, systematic reviews) are made more difficult or even impossible. For example, 32 studies were excluded from a systematic review of wound dressings and topical agents for arterial ulcers [5] because they did not report results separately by entity. The authors point

out that a large proportion of these studies could have been included in the analyses if corresponding subgroup analyses had been available.

For clinical trials on medical devices, prospective registration in a suitable study registry (e.g., on ClinicalTrials.gov) and public access to study data (study protocol; study results) via results databases should therefore be made mandatory, as has been the case for medicinal products in the EU since 2012. In addition, there should be a publication requirement to make study data publicly available in a timely manner.

Patient-reported outcomes and adverse effects are not sufficiently taken into account in study planning

In studies in the therapeutic area of chronic wounds, many outcomes are recorded that are not (clearly) relevant to patients. For example, partial wound closure is often recorded and described as a surrogate for complete wound closure without reference to corresponding analyses to demonstrate the validity of the surrogate outcome. Even on the basis of a systematic search, no corresponding surrogate validation study was identified. As part of the commenting procedure on the preliminary report, Lammert 2024 [127] was presented as a further publication examining the surrogate of partial wound closure. Similar to the analysis by Gwilym 2023 [118] described in this rapid report, Lammert 2024 does not meet the necessary requirements for surrogate validation. Reasons for this include the lack of suitable, high-quality RCTs, the inclusion of observational studies, the purely qualitative summary of study results, and the lack of presentation of correlations.

Complete wound healing is usually the primary treatment goal of wound treatment, and products that achieve this in defined therapeutic situations should have higher reimbursement than products for which such a therapeutic effect has not been proven. However, this does not mean that treatment effects can be derived exclusively on the basis of complete wound healing. By linking the effects of partial wound closure to an outcome that is directly relevant to the patient, such as social participation, a substantial improvement in the patient's life situation can be demonstrated in certain treatment situations.

However, this requires that patient-reported outcomes on morbidity, activities of daily living, social participation, or health-related quality of life are also recorded in intervention studies on wound treatment, which is currently rarely the case [128]. This is particularly necessary because the quality of life of patients with chronic wounds is potentially substantially reduced due to wound pain and the resulting mobility restrictions, sleep disorders, difficulties with personal hygiene, or reduced food intake [18]. In addition, patients may experience anxiety, frustration, and a reduction in social contacts, even leading to social isolation [41]. The relevance of these factors also became clear in discussions with affected patients during the preparation of the report. Improving symptoms, social participation, and health-related

quality of life is therefore a central treatment goal in the treatment of chronic wounds and should be a central component of clinical trials — the demonstration of benefit based on these outcomes is fundamentally possible. A few validated instruments are already available for this purpose. The situation is similar for outcomes on adverse effects. These are also often not systematically recorded, which means that it is not possible to adequately weigh up the benefits and harms of the treatments under investigation. Here, too, established coding systems and standardized analyses are already available that can also be used in wound treatment studies. An internationally agreed set of standard outcomes (core outcome set) could be used to standardize data collection in a modular way, both across wound types and for specific wound types. This would improve the comparability of study results and also facilitate the performance of meta-analyses. No such core outcome set exists at present.

In summary, chronic wounds represent a relevant health problem in Germany. Large parts of this therapeutic area are unexplored, and there is therefore a substantial need for research. The future requirement to demonstrate the benefit of “other wound treatment products” (SPzW) represents an opportunity to improve evidence-based care for patients with chronic wounds.

7 Conclusion

This report provides recommendations for the planning and conduct of healthcare-relevant studies in the therapeutic area of chronic wounds. Key points include the definition of a treatment protocol for the test and control interventions and for any concomitant treatments as well as the definition of an appropriate observation period. Even when investigating interventions with short-term treatment goals, a sufficiently long observation period should be planned in order to be able to rule out negative effects on the overarching treatment goal of complete wound healing or a substantial improvement in the patient's life situation with sufficient certainty.

Patients, study staff, and outcome assessors should be blinded. Mandatory participant information and education about the potential benefits or harms of the treatment options used in the study should be provided in a neutral manner. In addition to the outcome of complete wound closure, the recording of patient-reported outcomes on morbidity, activities of daily living, social participation, health-related quality of life, and adverse effects is particularly important. Consistent implementation of these recommendations will substantially improve the evidence base for the treatment of chronic wounds and thus also the care of patients.

Complete wound closure is usually the primary treatment goal, but in some situations, partial wound closure can also mean a substantial improvement in the patient's life situation. However, the reduction in wound size alone is not usually sufficient to justify a benefit. For example, without knowledge and evaluation of the specific wound characteristics, it is unclear what a 50 percent reduction in wound area means for patients and whether this change is perceived as a noticeable improvement in their respective life situation. In order to derive a benefit, it must therefore be sufficiently certain that partial wound closure has a direct impact on patient-relevant aspects, in particular improvements in health-related quality of life, activities of daily living, pain, and a noticeable change in a distressing wound characteristic (e.g., ulceration) that goes beyond size. To this end, the achievement of partial wound closure in clinical trials can be linked to the achievement of at least one directly patient-relevant, temporally-associated event.

Suitable studies that examine the validity of the outcome of partial wound closure as a surrogate for patient-relevant outcomes and meet the requirements for a surrogate validation study are not yet available. This rapid report therefore presents a proposal for the planning of a surrogate validation study.

References for English extract

Please see full rapid report for full reference list.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 06.10.2023]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

2. AWMF. S1-Leitlinie Pyoderma gangrenosum [online]. 2020 [Accessed: 01.10.2024]. URL: https://register.awmf.org/assets/guidelines/013-091l_S1_Pyoderma-gangrenosum_2020-10_1.pdf.

3. AWMF. Lokaltherapie schwerheilender und/oder chronischer Wunden aufgrund von peripherer arterieller Verschlusskrankheit, Diabetes mellitus oder chronischer venöser Insuffizienz; Evidenzbericht [online]. 2023 [Accessed: 29.05.2024]. URL: https://register.awmf.org/assets/guidelines/091-001e_S3_Lokaltherapie-schwerheilender-chronischer-Wunden_2023-11.pdf.

4. Beier JP, Koppert W, Hümmer P et al. Die chirurgische Wundversorgung beim Kind. CHAZ 2007; 8(9): 389-398.

5. Broderick C, Pagnamenta F, Forster R. Dressings and topical agents for arterial leg ulcers. Cochrane Database Syst Rev 2020; 1(1): Cd001836. https://doi.org/10.1002/14651858.CD001836.pub4.

6. Brolmann FE, Eskes AM, Sumpio BE et al. Fundamentals of randomized clinical trials in wound care: reporting standards. Wound Repair Regen 2013; 21(5): 641-647. https://doi.org/10.1111/wrr.12087.

7. Buchberger B, Follmann M, Freyer D et al. Bedeutung von Wachstumsfaktoren für die Behandlung von chronischen Wunden am Beispiel des diabetischen Fußulcus [online]. 2009 [Accessed: 30.09.2024]. URL: https://portal.dimdi.de/de/hta/hta_berichte/hta262_bericht_de.pdf.

8. Bull RH, Clements D, Collarte AJ et al. A Novel Randomized Trial Protocol for Evaluating Wound Healing Interventions. Adv Wound Care 2023; 12(12): 671-679. https://doi.org/10.1089/wound.2023.0058.

9. CADTH. Antimicrobial or Antiseptic Cleansers for Wounds [online]. 2023 [Accessed: 29.05.2024]. URL: https://www.cda-amc.ca/sites/default/files/pdf/htis/2023/RC1488%20Wound%20Cleansers.pdf.

10. Carter MJ, DaVanzo J, Haught R et al. Chronic wound prevalence and the associated cost of treatment in Medicare beneficiaries: changes between 2014 and 2019. J Med Econ 2023; 26(1): 894-901. https://doi.org/10.1080/13696998.2023.2232256.

11. Deutsche Gesellschaft für Angiologie, Gesellschaft für Gefäßmedizin. S3-Leitlinie zur Diagnostik, Therapie und Nachsorge der peripheren arteriellen Verschlusskrankheit [online]. 2024 [Accessed: 01.10.2024]. URL: https://register.awmf.org/assets/guidelines/065-003l_S3_Diagnostik-Therapie-Nachsorge-periphere-arterielle-Verschlusskrankheit_2024-09_1.pdf.

12. Deutsche Gesellschaft für Kinderchirurgie. S1 Leitlinie Wunden und Wundbehandlung im Kindesalter [online]. 2021 [Accessed: 01.10.2024]. URL: https://register.awmf.org/assets/guidelines/006-129l_S1_Wunden_Wundbehandlung_2021-08.pdf.

13. Deutsche Gesellschaft für Palliativmedizin. Exulzerierende Wunden; Leitlinien der DGP Sektion Pflege [online]. 2020 [Accessed: 09.10.2024]. URL: https://www.dgpalliativmedizin.de/images/stories/pdf/Leitlinie_exulzerierende_Wunden_end.pdf.

14. Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF. Palliativmedizin für Patienten mit einer nicht-heilbaren Krebserkrankung [online]. 2020 [Accessed: 01.10.2024]. URL: https://register.awmf.org/assets/guidelines/128-001OLl_S3_Palliativmedizin_2020-09_02.pdf.

15. Deutschen Gesellschaft für Phlebologie und Lymphologie. Diagnostik und Therapie des Ulcus cruris venosum [online]. 2024 [Accessed: 01.10.2024]. URL: https://www.awmf.org/service/awmf-aktuell/diagnostik-und-therapie-des-ulcus-cruris-venosum.

16. Deutschen Gesellschaft für Verbrennungsmedizin. Behandlung thermischer Verletzungen des Erwachsenen [online]. 2021 [Accessed: 01.10.2024]. URL: https://register.awmf.org/assets/guidelines/044-001l_S2k_Behandlung-thermischer-Verletzungen-des-Erwachsenen_2021-07.pdf.

17. Deutschen Gesellschaft für Wundheilung und Wundbehandlung. Lokaltherapie schwerheilender und/oder chronischer Wunden aufgrund von peripherer arterieller Verschlusskrankheit, Diabetes Mellitus oder chronischer venöser Insuffizienz; S3-Leitlinie 091-001, [online]. 2023 [Accessed: 29.05.2024]. URL: https://register.awmf.org/assets/guidelines/091-001l_S3_Lokaltherapie-schwerheilender-chronischer-Wunden_2023-11.pdf.

18. Deutsches Netzwerk für Qualitätsentwicklung in der Pflege. Expertenstandard Pflege von Menschen mit chronischen Wunden. Osnabrück: Hochschule Osnabrück; 2015.

19. Diener H, Eberlein T, Munter KC et al. Konzeption einer klinischen Studie zum Nachweis des therapeutischen Nutzens eines sonstigen Produktes zur Wundbehandlung. MMW Fortschr Med 2024; 166(Suppl 5): 17-26. https://doi.org/10.1007/s15006-024-4090-1.

20. Dissemond J, Gerber V, Lobmann R et al. Therapeutischer Index für Lokale Infektionen; TILI-Score Version 2.0. Wund-Management 2021; 15(03): 123-126.

21. Dissemond J, Kröger K, Initiative Chronische Wunden. Chronische Wunden; Diagnostik, Therapie, Versorgung. München: Elsevier; 2024.

22. Driver VR, Gould LJ, Dotson P et al. Evidence supporting wound care end points relevant to clinical practice and patients' lives. Part 2. Literature survey. Wound Repair Regen 2019; 27(1): 80-89. https://doi.org/10.1111/wrr.12676.

23. Driver VR, Gould LJ, Dotson P et al. Identification and content validation of wound therapy clinical endpoints relevant to clinical practice and patient values for FDA approval. Part 1. Survey of the wound care community. Wound Repair Regen 2017; 25(3): 454-465. https://doi.org/10.1111/wrr.12533.

24. DynaMed. Diabetic Foot Ulcer [online]. 2024 [Accessed: 01.10.2024]. URL: https://www.dynamed.com/condition/diabetic-foot-ulcer#GUID-5FBDACD7-0960-4147-882E-BE1C6E378496.

25. European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel, Pan Pacific Pressure Injury Alliance. Prevention and Treatment of Pressure Ulcers/Injuries; Clinical Practice Guideline; The International Guideline 2019 [online]. 2019 [Accessed: 29.05.2024]. URL: https://internationalguideline.com/s/CPG2019edition-digital-Nov2023version.pdf.

26. Food and Drug Administration. Guidance Document Chronic Cutaneous Ulcer and Burn Wounds; Developing Products for Treatment [online]. 2006 [Accessed: 01.10.2024]. URL: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/chronic-cutaneous-ulcer-and-burn-wounds-developing-products-treatment.

27. Food and Drug Administration. Guidance Document Diabetic Foot Infections; Developing Drugs for Treatment [online]. 2024 [Accessed: 29.08.2024]. URL: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diabetic-foot-infections-developing-drugs-treatment.

28. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Birkenrindenextrakt (Wundbehandlung bei Epidermolysis bullosa (ab 6 Monaten)) [online]. 2023 [Accessed: 29.08.2024]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/876/.

29. Gemeinsamer Bundesausschuss. Erprobungs-Richtlinie; Kaltplasmabehandlung bei chronischen Wunden [online]. 2023 [Accessed: 29.08.2024]. URL: https://www.g-ba.de/beschluesse/5889/.

30. Gesellschaft für Paraplegie. S1-Leitlinie Querschnittspezifische Dekubitusbehandlung und -prävention [online]. 2017 [Accessed: 01.10.2024]. URL: https://register.awmf.org/de/leitlinien/detail/179-008.

31. Gethin G, Vellinga A, McIntosh C et al. Systematic review of topical interventions for the management of odour in patients with chronic or malignant fungating wounds. J Tissue Viability 2023; 32(1): 151-157. https://doi.org/10.1016/j.jtv.2022.10.007.

32. Gottrup F, Apelqvist J, Price P et al. Outcomes in controlled and comparative studies on non-healing wounds; recommendations to improve the quality of evidence in wound management. J Wound Care 2010; 19(6): 237-268. https://doi.org/10.12968/jowc.2010.19.6.48471.

33. Herrod PJ, Doleman B, Hardy EJ et al. Dressings and topical agents for the management of open wounds after surgical treatment for sacrococcygeal pilonidal sinus. Cochrane Database Syst Rev 2022; 5(5): Cd013439. https://doi.org/10.1002/14651858.CD013439.pub2.

34. Heyer K, Herberger K, Protz K et al. Epidemiology of chronic wounds in Germany: Analysis of statutory health insurance data. Wound Repair Regen 2016; 24(2): 434-442. https://doi.org/10.1111/wrr.12387.

35. Hu Z, Wang S, Yang H et al. Efficacy and safety of platelet-rich plasma in the treatment of venous ulcers: A systematic review and meta-analysis of randomized controlled trials. Int Wound J 2024; 21(2): e14736. https://doi.org/10.1111/iwj.14736.

36. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Vakuumversiegelungstherapie von Wunden mit intendierter sekundärer Wundheilung; Abschlussbericht [online]. 2019 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/n17-01a_abschlussbericht_vakuumversiegelungstherapie-von-wunden-mit-intendierter-sekundaerer-wundheilung_v1-1.pdf.

37. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Vakuumversiegelungstherapie von Wunden mit intendierter primärer Wundheilung; Abschlussbericht [online]. 2019 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/n17-01b_vakuumversiegelungstherapie-von-wunden-primaere-wundheilung_abschlussbericht_v1-0.pdf.

38. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Kaltplasma zur Wundbehandlung; Potenzialbewertung [online]. 2021 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/e21-03_kaltplasma-zur-wundbehandlung_potenzialbewertung_v1-0.pdf.

39. Jeffcoate WJ, Bus SA, Game FL et al. Reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes: required details and markers of good quality. Lancet Diabetes Endocrinol 2016; 4(9): 781-788. https://doi.org/10.1016/S2213-8587(16)30012-2.

40. Jull AB, Cullum N, Dumville JC et al. Honey as a topical treatment for wounds. Cochrane Database Syst Rev 2015; (3). https://doi.org/10.1002/14651858.CD005083.pub4.

41. Klein TM, Andrees V, Kirsten N et al. Social participation of people with chronic wounds; A systematic review. Int Wound J 2021; 18(3): 287-311. https://doi.org/https://doi.org/10.1111/iwj.13533.

42. Köster I, Schubert I. Epidemiologie und Versorgung von Patienten mit chronischen Wunden; Eine Analyse auf der Basis der Versichertenstichprobe AOK Hessen/KV Hessen [online]. 2015 [Accessed: 01.10.2024]. URL: https://www.bvmed.de/download/pmv-zusammenfassung-der-ergebnisse.

43. Li S, Xing F, Yan T et al. The Efficiency and Safety of Platelet-Rich Plasma Dressing in the Treatment of Chronic Wounds: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Pers Med 2023; 13(3). https://doi.org/10.3390/jpm13030430.

44. Lipsky BA, Senneville E, Abbas ZG et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update). Diabetes Metab Res Rev 2020; 36 Suppl 1(1520-7560 (Electronic)): e3280. https://doi.org/10.1002/dmrr.3280.

45. Liu Z, Dumville JC, Hinchliffe RJ et al. Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus. Cochrane Database Syst Rev 2018; 10(10): CD010318. https://doi.org/10.1002/14651858.CD010318.pub3.

46. Luo Y, Li L, Zhao P et al. Effectiveness of silver dressings in the treatment of diabetic foot ulcers: a systematic review and meta-analysis. J Wound Care 2022; 31(11): 979-986. https://doi.org/10.12968/jowc.2022.31.11.979.

47. National Institute for Health Care Excellence. The Debrisoft monofilament debridement pad for use in acute or chronic wounds [online]. 2014 [Accessed: 01.10.2024]. URL: https://www.nice.org.uk/guidance/mtg17.

48. National Institute for Health Care Excellence. Oxyzyme and Iodozyme 2-layer hydrogel wound dressings with iodine for treating chronic wounds [online]. 2014 [Accessed: 01.10.2024]. URL: https://www.nice.org.uk/advice/mib11.

49. Norman G, Shi C, Goh EL et al. Negative pressure wound therapy for surgical wounds healing by primary closure. Cochrane Database Syst Rev 2022; 4(4): Cd009261. https://doi.org/10.1002/14651858.CD009261.pub7.

50. Norman G, Westby MJ, Rithalia AD et al. Dressings and topical agents for treating venous leg ulcers. Cochrane Database Syst Rev 2018; 6(6): Cd012583. https://doi.org/10.1002/14651858.CD012583.pub2.

51. Nussbaum SR, Carter MJ, Fife CE et al. An Economic Evaluation of the Impact, Cost, and Medicare Policy Implications of Chronic Nonhealing Wounds. Value Health 2018; 21(1): 27-32. https://doi.org/10.1016/j.jval.2017.07.007.

52. Ontario Health. Skin substitutes for adults with diabetic foot ulcers and venous leg ulcers [online]. 2021 [Accessed: 01.10.2024]. URL: https://www.hqontario.ca/Portals/0/Documents/evidence/reports/hta-skin-substitutes-for-adults-with-diabetic-foot-ulcers-and-venous-leg-ulcers.pdf.

53. Pomponio G, Tedesco S, Peghetti A et al. Improving the quality of clinical research on chronic wound infection treatment: expert-based recommendations. J Wound Care 2019; 28(Sup1): S26-S31. https://doi.org/10.12968/jowc.2019.28.Sup1.S26.

54. Price P, Gottrup F, Abel M. Ewma Study Recommendations: For Clinical Investigations in Leg Ulcers and Wound Care. J Wound Care 2014; 23 Suppl 5: S1-S36. https://doi.org/10.12968/jowc.2014.23.Sup5c.S1.

55. Raeder K, Jachan DE, Muller-Werdan U et al. Prevalence and risk factors of chronic wounds in nursing homes in Germany; A Cross-Sectional Study. Int Wound J 2020; 17(5): 1128-1134. https://doi.org/10.1111/iwj.13486.

56. Raeder K, Strube-Lahmann S, Muller-Werdan U et al. Prävalenz und Einflussfaktoren von chronischen Wunden bei Klienten von ambulanten Pflegediensten in Deutschland. Z Evid Fortbild Qual Gesundhwes 2019; 140: 14-21. https://doi.org/10.1016/j.zefq.2019.01.001.

57. Reinboldt-Jockenhöfer F, Babadagi Z, Hoppe HD et al. Association of wound genesis on varying aspects of health-related quality of life in patients with different types of chronic wounds: Results of a cross-sectional multicentre study. Int Wound J 2021; 18(4): 432-439. https://doi.org/10.1111/iwj.13543.

58. Ribeiro CT, Dias FA, Fregonezi GA. Hydrogel dressings for venous leg ulcers. Cochrane Database Syst Rev 2022; 8(8): Cd010738. https://doi.org/10.1002/14651858.CD010738.pub2.

59. Roehrs H, Stocco JGD, Pott F et al. Dressings and topical agents containing hyaluronic acid for chronic wound healing. Cochrane Database Syst Rev 2023; (7): CD012215. https://doi.org/10.1002/14651858.CD012215.pub2.

60. Schulz KF, Grimes DA. Reihe Epidemiologie 8; Verblindung in randomisierten Studien; Wie man verdeckt, wer was erhalten hat. Z Arztl Fortbild Qualitatssich 2007; 101(9): 630-637. https://doi.org/https://doi.org/10.1016/j.zgesun.2007.09.024.

61. Shi C, Dumville JC, Cullum N et al. Compression bandages or stockings versus no compression for treating venous leg ulcers. Cochrane Database Syst Rev 2021; (7): CD013397. https://doi.org/10.1002/14651858.CD013397.pub2.

62. Shi JY, Gao Y, Tian JH et al. Negative pressure wound therapy for treating pressure ulcers. Cochrane Database Syst Rev 2023; (5). https://doi.org/10.1002/14651858.CD011334.pub3.

63. Snyder D, Sullivan N, Margolis D et al. Skin Substitutes for Treating Chronic Wounds; Technology Assessment Program; Technical Brief; Project ID: WNDT0818 [online]. 2020 [Accessed: 29.05.2024]. URL: https://www.ncbi.nlm.nih.gov/books/NBK554220/.

64. Sonnad SS, Goldsack JC, Mohr P et al. Methodological recommendations for comparative research on the treatment of chronic wounds. J Wound Care 2013; 22(9): 470-480. https://doi.org/10.12968/jowc.2013.22.9.470.

65. Stürmer EK, Dissemond J. Evidenz in der lokalen Therapie chronischer Wunden; Was ist gesichert? Phlebologie 2022; 51(02): 79-87. https://doi.org/10.1055/a-1755-4959.

66. Veličković VM, Macmillan T, Lones E et al. Systematic review and quality assessment of clinical and economic evidence for superabsorbent wound dressings in a population with chronic ulcers. Int Wound J 2024; 21(3): e14750. https://doi.org/10.1111/iwj.14750.

67. Vollenweider D, Ebneter I, Mayer D et al. Dealing with heterogeneous populations in randomized wound trials: challenges and potential solutions. Wound Repair Regen 2012; 20(4): 466-472. https://doi.org/10.1111/j.1524-475X.2012.00806.x.

68. Zhao H, Wu Y, Xie Y et al. Hydrogel dressings for diabetic foot ulcer: A systematic review and meta-analysis. Diabetes Obes Metab 2024; 26(6): 2305-2317. https://doi.org/10.1111/dom.15544.

69. Amboss. Akute Wunden und Wundverschluss [online]. 2024 [Accessed: 16.12.2024]. URL: https://next.amboss.com/de/article/ph0LUf?q=wunde.

70. AWMF. S2k-Leitlinie Medizinische Kompressionstherapie der Extremitäten mit Medizinischem Kompressionsstrumpf (MKS), Phlebologischem Kompressionsverband (PKV) und Medizinischen adaptiven Kompressionssystemen (MAK) [online]. 2018 [Accessed: 04.12.2024]. URL: https://register.awmf.org/de/leitlinien/detail/037-005.

71. UpToDate. Basic principles of wound healing [online]. 2024 [Accessed: 16.12.2024]. URL: https://www.uptodate.com/contents/basic-principles-of-wound-healing/.

72. UpToDate. Risk factors for impaired wound healing and wound complications [online]. 2024 [Accessed: 16.12.2024]. URL: https://www.uptodate.com/contents/risk-factors-for-impaired-wound-healing-and-wound-complications.

73. Tisch T, Nolting HD. Versorgungsreport 2024; Chronische Wunden - Versorgungssituation und Optimierungspotenziale [online]. 2024 [Accessed: 12.02.2025]. URL: https://caas.content.dak.de/caas/v1/media/86682/data/5420fe7fee043eb318f60327035197e9/versorgungsreport-2024-chronische-wunden-report.pdf.

74. Dissemond J, Bültemann A, Gerber V et al. Der Begriff Ulcus cruris mixtum sollte heute nicht mehr verwendet werden. Die Dermatologie 2023; 74(7): 555-559. https://doi.org/10.1007/s00105-023-05129-2.

75. Isoherranen K, O'Brien JJ, Barker J et al. Atypical wounds. Best clinical practice and challenges. J Wound Care 2019; 28(Sup6): S1-S92. https://doi.org/10.12968/jowc.2019.28.Sup6.S1.

76. Prodinger C, Laimer M. Neue Lokal- und Systemtherapien bei Epidermolysis bullosa. hautnah 2024; 23(1): 43-49. https://doi.org/10.1007/s12326-024-00627-z.

77. Snyder RJ, Cardinal M, Dauphinee DM et al. A post-hoc analysis of reduction in diabetic foot ulcer size at 4 weeks as a predictor of healing by 12 weeks. Ostomy Wound Management 2010; 56(3): 44-50.

78. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001; 69(3): 89-95. https://doi.org/10.1067/mcp.2001.113989.

79. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research et al. Guidance for industry; Chronic cutaneous ulcer and burn wounds; developing products for treatment. Wound Repair Regen 2001; 9(4): 258-268.

80. Cardinal M, Eisenbud DE, Phillips T et al. Early healing rates and wound area measurements are reliable predictors of later complete wound closure. Wound Repair Regen 2008; 16(1): 19-22. https://doi.org/10.1111/j.1524-475X.2007.00328.x.

81. Coerper S, Beckert S, Kuper MA et al. Fifty percent area reduction after 4 weeks of treatment is a reliable indicator for healing--analysis of a single-center cohort of 704 diabetic patients. J Diabetes Complications 2009; 23(1): 49-53. https://doi.org/10.1016/j.jdiacomp.2008.02.001.

82. Gelfand JM, Hoffstad O, Margolis DJ. Surrogate endpoints for the treatment of venous leg ulcers. J Invest Dermatol 2002; 119(6): 1420-1425. https://doi.org/10.1046/j.1523-1747.2002.19629.x.

83. Kantor J, Margolis DJ. A multicentre study of percentage change in venous leg ulcer area as a prognostic index of healing at 24 weeks. Br J Dermatol 2000; 142(5): 960-964. https://doi.org/10.1046/j.1365-2133.2000.03478.x.

84. Patry J, Tourigny A, Mercier MP et al. Outcomes and prognosis of diabetic foot ulcers treated by an interdisciplinary team in Canada. Int Wound J 2021; 18(2): 134-146. https://doi.org/10.1111/iwj.13505.

85. Phillips TJ, Machado F, Trout R et al. Prognostic indicators in venous ulcers. J Am Acad Dermatol 2000; 43(4): 627-630. https://doi.org/10.1067/mjd.2000.107496.

86. Valenzuela-Silva CM, Tuero-Iglesias AD, Garcia-Iglesias E et al. Granulation response and partial wound closure predict healing in clinical trials on advanced diabetes foot ulcers treated with recombinant human epidermal growth factor. Diabetes Care 2013; 36(2): 210-215. https://doi.org/10.2337/dc12-1323.

87. Cleeland CS. The Brief Pain Inventory; User Guide [online]. 2009 [Accessed: 21.10.2024]. URL: https://www.mdanderson.org/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf.

88. European Medicines Agency. Guideline on the clinical development of medicinal products intended for the treatment of pain [online]. 2016 [Accessed: 30.09.2024]. URL: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-development-medicinal-products-intended-treatment-pain-first-version_en.pdf.

89. European Medicines Agency. Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections [online]. 2022 [Accessed: 01.10.2024]. URL: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-medicinal-products-indicated-treatment-bacterial-infections-revision-3_en.pdf.

90. Katz S, Ford AB, Moskowitz RW et al. Studies of Illness in the Aged. The Index of Adl: A Standardized Measure of Biological and Psychosocial Function. JAMA 1963; 185: 914-919. https://doi.org/10.1001/jama.1963.03060120024016.

91. Lawton MP, Brody EM. Assessment of Older People; Self-Maintaining and Instrumental Activities of Daily Living1. The Gerontologist 1969; 9(3_Part_1): 179-186. https://doi.org/10.1093/geront/9.3_Part_1.179.

92. Douglas H, Georgiou A, Westbrook J. Social participation as an indicator of successful aging; an overview of concepts and their associations with health. Aust Health Rev 2017; 41(4): 455-462. https://doi.org/10.1071/AH16038.

93. Gaasterland CM, Jansen-van der Weide MC, Weinreich SS et al. A systematic review to investigate the measurement properties of goal attainment scaling, towards use in drug trials. BMC Med Res Methodol 2016; 16: 99. https://doi.org/10.1186/s12874-016-0205-4.

94. Kiresuk TJ, Sherman RE. Goal attainment scaling; A general method for evaluating comprehensive community mental health programs. Community Ment Health J 1968; 4(6): 443-453. https://doi.org/10.1007/BF01530764.

95. Maruish ME. User's manual for the SF-36v2 Health Survey. Lincoln: QualityMetric; 2011.

96. Mapi Research Trust. PROQOLID: Patient-Reported Outcome and Quality of Life Instruments Database [online]. [Accessed: 07.03.2025]. URL: https://eprovide.mapi-trust.org/.

97. COSMIN. COSMIN Database of Systematic Reviews of Outcome Measurement Instruments [online]. [Accessed: 07.03.2025]. URL: https://www.cosmin.nl/tools/database-systematic-reviews/.

98. Farias Alves Yamada B, Conceição de Gouveia Santos VL. Development and validation of Ferrans & Powers Quality of Life Index: wound version. Rev Esc Enferm USP 2009; 43(spe): 1103-1111. Original Article. https://doi.org/10.1590/S0080-62342009000500015.

99. Palfreyman S, Michaels J, Brazier J. Development of a tool to examine the effect of venous ulcers on patients' quality of life. Nurs Stand 2007; 21(45): 57-58, 60, 62 passim. https://doi.org/10.7748/ns2007.07.21.45.57.c4585.

100. Augustin M, Herberger K, Rustenbach SJ et al. Quality of life evaluation in wounds: validation of the Freiburg Life Quality Assessment-wound module, a disease-specific instrument. Int Wound J 2010; 7(6): 493-501. https://doi.org/10.1111/j.1742-481X.2010.00732.x.

101. ORGAMed. Assessmentinstrumente zur Erfassung der Lebensqualität von Patienten mit chronischen Wunden [online]. [Accessed: 07.04.2025]. URL: https://www.orgamed-dortmund.de/assets/uploads/web/files/fachbeitraege/lebensqualitat2-protz.pdf.

102. Blome C, Baade K, Debus ES et al. The "Wound-QoL": a short questionnaire measuring quality of life in patients with chronic wounds based on three established disease-specific instruments. Wound Repair Regen 2014; 22(4): 504-514. https://doi.org/10.1111/wrr.12193.

103. Price P, Harding K. Cardiff Wound Impact Schedule: the development of a condition-specific questionnaire to assess health-related quality of life in patients with chronic wounds of the lower limb. Int Wound J 2004; 1(1): 10-17. https://doi.org/10.1111/j.1742-481x.2004.00007.x.

104. Debus ES, Faller H, Spech E et al. Lebensqualität bei arteriellen und venösen Ulcera cruris; Einführung eines krankheitsspezifischen Messinstruments. Gefässchirurgie 2005; 10(2): 99-108. https://doi.org/10.1007/s00772-005-0390-7.

105. Engelhardt M, Spech E, Diener H et al. Validation of the disease-specific quality of life Wuerzburg Wound Score in patients with chronic leg ulcer. Vasa 2014; 43(5): 372-379. https://doi.org/10.1024/0301-1526/a000378.

106. Spech E. Lebensqualität bei Patienten mit chronisch venösen und arteriellen Ulcera cruris [online]. 2003 [Accessed: 23.07.2024]. URL: https://opus.bibliothek.uni-wuerzburg.de/opus4-wuerzburg/frontdoor/index/index/docId/604.

107. International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use. Clinical Safety Data Management; Definitions And Standards For Expedited Reporting E2A; Ich Harmonised Tripartite Guideline [online]. 1994 [Accessed: 06.04.2017]. URL: https://database.ich.org/sites/default/files/E2A_Guideline.pdf.

108. Thomas DR, Rodeheaver GT, Bartolucci AA et al. Pressure ulcer scale for healing: derivation and validation of the PUSH tool. The PUSH Task Force. Adv Wound Care 1997; 10(5): 96-101.

109. Hoffmann F, Kaiser T, Apfelbacher C et al. Erratum; Versorgungsnahe Daten zur Evaluation von Interventionseffekten: Teil 2 des Manuals. Gesundheitswesen 2021; 83(6): e40. https://doi.org/10.1055/a-1516-8823.

110. Friede T, Kieser M. A comparison of methods for adaptive sample size adjustment. Stat Med 2001; 20(24): 3861-3873. https://doi.org/10.1002/sim.972.

111. Bauer P, Bretz F, Dragalin V et al. Twenty-five years of confirmatory adaptive designs; opportunities and pitfalls. Stat Med 2016; 35(3): 325-347. https://doi.org/10.1002/sim.6472.

112. Dimairo M, Pallmann P, Wason J et al. The Adaptive designs CONSORT Extension (ACE) statement; a checklist with explanation and elaboration guideline for reporting randomised trials that use an adaptive design. BMJ 2020; 369: m115. https://doi.org/10.1136/bmj.m115.

113. Prentice RL. Surrogate endpoints in clinical trials; Definition and operational criteria. Stat Med 1989; 8(4): 431-440. https://doi.org/10.1002/sim.4780080407.

114. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Aussagekraft von Surrogatparametern in der Onkologie; Rapid Report, A10-05 [online]. 2011 [Accessed: 01.10.2024]. URL: https://www.iqwig.de/download/A10-05_Rapid_Report_Version_1-1_Surrogatendpunkte_in_der_Onkologie.pdf.

115. Manyara AM, Davies P, Stewart D et al. Reporting of surrogate endpoints in randomised controlled trial protocols (SPIRIT-Surrogate); extension checklist with explanation and elaboration. BMJ 2024; 386: e078525. https://doi.org/10.1136/bmj-2023-078525.

116. Manyara AM, Davies P, Stewart D et al. Reporting of surrogate endpoints in randomised controlled trial reports (CONSORT-Surrogate); extension checklist with explanation and elaboration. BMJ 2024; 386: e078524. https://doi.org/10.1136/bmj-2023-078524.

117. Xie W, Halabi S, Tierney JF et al. A Systematic Review and Recommendation for Reporting of Surrogate Endpoint Evaluation Using Meta-analyses. JNCI Cancer Spectr 2019; 3(1): pkz002. https://doi.org/10.1093/jncics/pkz002.

118. Gwilym BL, Mazumdar E, Naik G et al. Initial Reduction in Ulcer Size As a Prognostic Indicator for Complete Wound Healing: A Systematic Review of Diabetic Foot and Venous Leg Ulcers. Adv Wound Care (New Rochelle) 2023; 12(6): 327-338. https://doi.org/10.1089/wound.2021.0203.

119. Burzykowski T, Buyse M. Surrogate threshold effect: an alternative measure for meta-analytic surrogate endpoint validation. Pharm Stat 2006; 5(3): 173-186. https://doi.org/10.1002/pst.207.

120. Burzykowski T, Molenberghs G, Buyse M. The Evaluation of Surrogate Endpoints. New York: Springer; 2005.

121. Collier W, Haaland B, Inker L et al. Handling missing within-study correlations in the evaluation of surrogate endpoints. Stat Med 2023; 42(26): 4738-4762. https://doi.org/10.1002/sim.9886.

122. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Boceprevir; Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2011 [Accessed: 28.03.2025]. URL: https://www.iqwig.de/download/a11-17_boceprevir_nutzenbewertung_gemaess_35a_sgb_v.pdf.

123. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Rilpivirin; Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2012 [Accessed: 28.03.2025]. URL: https://www.iqwig.de/download/a12-04_rilpivirin_nutzenbewertung_35a_sgb_v.pdf.

124. Augustin M. Praxisbeispiele zu klinischen Studien mit Medizinprodukten und deren Anwendung: Wundversorgung. Z Evid Fortbild Qual Gesundhwes 2012; 106(5): 347-353. https://doi.org/10.1016/j.zefq.2012.05.015.

125. Das Europäischen Parlament, Der Rat der Europäischen Union. Verordnungen; Verordnung (EU) 2017/745 des Europäischen Parlaments und des Rates vom 5. April 2017 über Medizinprodukte, zur Änderung der Richtlinie 2001/83/EG, der Verordnung (EG) Nr. 178/2002 und der Verordnung (EG) Nr. 1223/2009 und zur Aufhebung der Richtlinien 90/385/EWG und 93/42/EWG des Rates [online]. 2017 [Accessed: 30.09.2024]. URL: http://data.europa.eu/eli/reg/2017/745/oj.

126. Gemeinsamer Bundesausschuss. Anlage V zum Abschnitt J der Arzneimittel-Richtlinie; Übersicht der verordnungsfähigen Medizinprodukte [online]. 2024 [Accessed: 14.10.2024]. URL: https://www.g-ba.de/downloads/83-691-955/AM-RL-V_2024-10-02.pdf.

127. Lammert A, Kiehlmeier S, Dissemond J et al. Percentage area reduction as surrogate for complete healing of hard-to-heal wounds; a review of clinical trials. J Wound Care 2024; 33(10): 737-755.

128. Miranda JS, Deonizio AP, Abbade JF et al. Quality of reporting of outcomes in trials of therapeutic interventions for pressure injuries in adults; a systematic methodological survey. Int Wound J 2021; 18(2): 147-157. https://doi.org/https://doi.org/10.1111/iwj.13506.

The full report (German version) is published under
https://www.iqwig.de/projekte/a24-61.html