EWMA STUDY RECOMMENDATIONS

FOR CLINICAL INVESTIGATIONS IN LEG ULCERS AND WOUND CARE

JWC journal of wound care

EWMA

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Contents

Chapter 1: Introduction

In 2010, the EWMA Patient Outcome Group (POG) published recommendations to improve the quality of evidence in wound management.[1] As a companion piece of work, the EWMA POG has worked to provide a series of user-friendly documents to assist those new to (or inexperienced in) research, in starting on the path to plan, conduct, interpret and disseminate findings from an investigation that will improve our understanding of clinical wound healing and raise the evidence level of the work undertaken in this important area. Given the range of wound types that clinicians are involved with, the POG has decided to limit the first of these to venous leg ulcers. In addition, as a European association, the focus will be on EU regulations and directives.

Relevant sources of information

1 Gottrup, F., Apelqvist, J., Price, P. 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.

2 **NICE Guidelines manual**
www.nice.org.uk/guidelinesmanual

Reporting guidelines:

RCT: CONSORT
www.consort-statement.org/

3 Moher, D., et al. Consort 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials; BMJ 2010; 340: c869.

4 Observational studies: STROBE

www.strobe-statement.org/

5 Systematic reviews: PRISMA

www.prisma-statement.org/

The target audience for this publication is hospital and community clinicians working collaboratively with other professions or with industry. In particular, it aims to provide a clinical study guideline for the novice researcher working within wound care (leg ulcers), but the guideline may also be relevant for article reviewers, or as a checklist for the experienced researcher. The text will take the format of a 'step-by-step' instruction manual to highlight activities to consider and outline frequent mistakes that many of us have made along the way, with the aim of helping novice researchers avoid making them, and improve the quality of studies that are undertaken. The emphasis will focus on Randomised Controlled Trials (RCTs) and cohort studies that are prospective (retrospective studies are not included). You can find an outline of different study designs in the Nice/UK: Guideline Manual 2009.[2] Numerous reporting guidelines exist for different study designs have been developed: When conducting a randomised trial, you should consult the CONSORT guideline.[3] Links to the CONSORT guideline as well as guidelines for observational studies (STROBE)[4] and systematic reviews/meta-analyses (PRISMA)[5] are provided in the reference and links column on the next page.

It would be very tempting to include all necessary documents in this text, but that would result in a heavy, dense textbook that may put people off doing research. Therefore, our approach will be to signpost relevant existing documents and provide links to websites and documents where regulation specific issues are thoroughly covered. The aim is to produce a user-friendly and practical resource.

The format will take the form of short chapters on different aspects of the research process, with many points made in bullet point format. It is not anticipated that researchers will read every page and the associated web links in order, but use it as a pathway through the process, with the text highlighting when it would be useful to take a detour into other resources to get additional information.

In some instances, we will provide you with a mark [!] to highlight points where extra attention is required. The first of these can be found on the right. It is really important that you check the ethical framework and regulations relevant to your country. We have tried to include key points whenever possible but all staff involved in clinical trials will need to be trained on the Good Clinical Practice principles. For example, the practical issues related to managing the ethical issues at a patient and data level can be found in ICH E6 (R1)[6] or the Declaration of Helsinki.[7] Relevant EU directives on medical devices and clinical trials can be found at the healthcare-related websites of the European Commission.[8,9]

The information is divided into chapters that reflect the different stages of the process; many chapters have multiple subsections so that you can easily find help with a specific issue. We hope that you will find this document useful in putting together your research plans and look forward to reading the papers at some point in the future as you contribute to the evidence base for improved wound healing outcomes.

N.B.: the terms "investigation" and "study" are used interchangeably throughout. "Investigation" is the common term used for regulatory medical device studies, while "study" is the more general term within academic research.

Relevant links related to ethical issues:

6 ICH E6 (R1) Guideline for Good Clinical Practice: Available at: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

7 WMA Declaration of Helsinki: Principles for Medical research involving Human Subjects
Available at: www.wma.net/en/30publications/10policies/b3/

EU directives on medical devices and clinical trials:

8 The Medical Device Directive (Council Directive 93/42/EEC), as amended by DIRECTIVE 2007/47/EC.
Available at: http://ec.europa.eu/health/medical-devices/regulatory-framework/index_en.htm

9 EU Directive 2001: Good clinical practice in the conduct of clinical trials.
Available at: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf

! All studies will need to fall under the ethical guidelines of the grant awarding body – make sure you look at the rules for the award before you start.
RCTs must be conducted within the EU Directive on Clinical Trials (Directive 2001/20/EC) and in line with the principles of Good Clinical Practice, which is an international quality standard based on the International Conference on Harmonisation (ICH).[6] All these guidelines are frequently updated; make sure you are using the most current version.

! If you are working collaboratively with industry on a project, you should look at the Eucomed web page on Ethics and Compliance.[10]

Chapter 2: Research Planning

This chapter includes three main sections that relate to planning your research – before you start collecting any data, and includes sections on formulating your research question or hypothesis; choosing the appropriate design; detailed methods to consider and planning how your investigation will be managed.

2.1 Research Questions and Hypotheses

Before you even start to think about the details of the 'how' and 'when' to conduct an investigation, you need to be very clear about the rationale for the investigation, and focus on the 'why'. Why are you doing this investigation? What are the unanswered questions that justify patient involvement, the time and the costs associated with such an investigation? If this is to be a clinical trial, does equipoise exist (i.e., are the existing data so uncertain that the research/clinical community are uncertain on whether a new or existing treatment is any better or worse than current standard treatment)?

A good lesson here is to make your research question is clearly defined as possible, as this will help in designing your investigation. If there is enough data from other studies available, you may be able to use a hypothesis that predicts the amount of difference you expect to see between interventions (a 20% difference is the convention we usually use as a potentially important difference) over a set time period. Getting the question right is crucial to the rest of the research process; in the worst case, you end up with the right answer to the wrong question and waste a lot of time and resources. You need a clear, concise and accurate question. Many people use the PICO method to help define their clinical research question, where P refers to the Patient, Population or Problem, I is Intervention, C refers to the comparator; and O represents the outcome.

The next step is to undertake a thorough literature search.[11] For this purpose, your research question should be broken into keywords and phrases. When doing so, you should try to identify all useful terms. When identifying relevant literature, it is important to evaluate and clarify the type and quality of papers and websites you review. For help with critiquing papers, see for example the Critical Appraisal Skills Programme (CASP).[12]

From the review of literature, you will be able to start considering the right type of design[13] to provide data to answer the research question or

Relevant sources of information

10 Eucomed, Ethics and Compliance.
Available at: www.eucomed.org/key-themes/ethics.

For a short introduction to literature search strategy and paper critique, please see:

11 Havard, L. How to conduct an effective and valid literature search. Nurs Times 2007; 103: 44, 32–33.
12 Critical Appraisal Skills Programme (CASP)
Available at: www.casp-uk.net

For an overview of typical study types, please see:

13 MEDDEV 2.7.1 Rev. 3, Guidelines on Medical Devices, Clinical Evaluation, Dec 2009

For a flow diagram illustrating parallel group trials, please see:

14 Schulz, K.F., Altman, D.G., Moher, D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010; 340: c332.

hypothesis. You may also identify existing data relevant for your research question. The best design to answer questions related to a causal relationship between treatment and out-comes is to use a RCT; however, these are expensive, time consuming and often require the involvement of multiple sites if they are to be of sufficient size to produce meaningful data, so you must consider the resources and infrastructure you have available to you. Within the RCT, you will need to be clear about how many groups you will include for comparison.[14] For example, will it just be a new treatment vs standard care? One of the difficulties in wound management studies is to define what is meant by 'standard care'; variation in practice across Europe is such that you cannot assume that what is standard care in one facility will be the same elsewhere. Ensuring that all centres and all staff involved with the investigation are educated on how 'standard care' is defined within an investigation is extremely important as otherwise, the comparisons become meaningless. In an investigation that will be used for regulatory purposes (i.e., to obtain data to acquire a licence for a new product), all such education/training will need to be recorded and documented.

If you are in a position to observe a whole cohort of patients in a structured way over a defined period of time (cohort study), you may be able to observe patterns in the data around the relationship between type of intervention and predefined outcomes, provided you can be sure to collect the data in a systematic and consistent way. While this document focuses on RCTs and cohort studies, there are a number of other designs that you may wish to review.[13]

From a regulatory point of view, there will be differences in approach to the design depending on whether or not you are investigating a product that is CE-marked (a mandatory conformity mark for all products on the market in the European Economic Market). In general, medical devices can be marketed only if their manufacturers have already obtained a CE marking.

! Frequent mistakes

Rushing to start the study before conducting a thorough review of the literature. You need to know:…

- ❑ What has already been done?
- ❑ What do we already know?
- ❑ What can you learn from the limitations of the studies already completed?

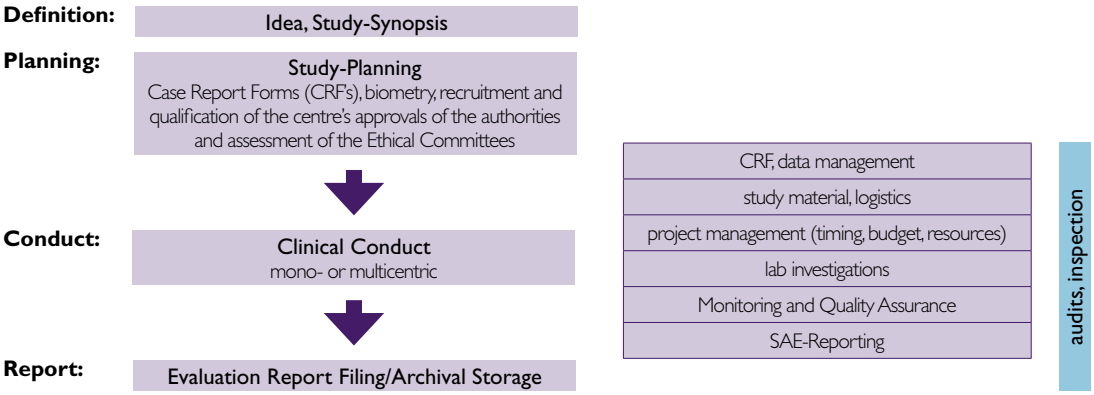
! To help define your clinical research question; remember PICO:

- ❑ P: Patients, Population or Problem
  - What are the characteristics of the patient or population?
  - What is the condition or disease you are interested in?
- ❑ I: Intervention or exposure
  - What do you want to do – treat, diagnose, observe?
- ❑ C: Comparison
  - What is the alternative to the intervention?
- ❑ O: Outcome
  - What are the relevant outcomes (e.g., healing, reduction of oedema)?

! Frequent mistakes

- ❑ Making the design too complex
- ❑ Not defining what you mean by 'standard care'
- ❑ Integrating too many primary outcome measures

Fig 1. Phases of a clinical investigation



2.2 Research design and methods

A clinical investigation plan contain different phases; Fig 1 provides an illustration of this process.

The following sections will list important aspects to consider with regards to the appropriate study design to use, selection of participants and study locations, interventions for each group of participants, choice of outcome measures, sample size, randomisation, blinding and statistical methods. The rationale for your choices should be described in the clinical investigation plan.[15]

For more information about the content and development of a clinical investigation plan, please see:
15 ISO 14155: 2011 (Annex A)

For an overview of typical study types, please see:
13 MEDDEV 2.7.1 Rev. 3, Guidelines on Medical Devices, Clinical Evaluation, Dec 2009

2.2.1 Methods: Study design

In overall terms, this guidance document focuses on RCTs and cohort studies.

RCTs are a superior methodology in the hierarchy of evidence in therapy, because they limit the potential for bias by randomly assigning one patient pool to an intervention and another patient pool to non-intervention/placebo or standard treatment. This minimises the chance that the incidence of confounding variables will differ between the two groups (i.e., that different patient variables in the groups will affect the outcome of the investigation).

However, it is important to note that RCTs may not be suitable in all cases and other methodologies could be much more suitable to investigate the study's objective.[12]

Different types of trial designs include parallel, factorial, multi-arm parallel, crossover and cluster trials.[13] If more than one intervention is planned for evaluation, the typical trial designs are:

- A parallel trial: usually a two group study where each participant is randomly assigned to a group,

and all the participants in the group receive (or do not receive) an intervention.[14]

- A factorial trial: each participant is randomly assigned to a group that receives a particular combination of interventions or non-interventions. Factorial trials require special considerations, particularly at the design and analysis stages.

In addition to the overall study design, it is important to define:

- The conceptual framework of the investigation – do you wish to demonstrate superiority/non-inferiority/equivalence of a treatment strategy or product?

- The allocation ratio of patients to the groups you are comparing.

Specific for RCTs

The key distinguishing feature of the RCT is that study subjects, after assessment of eligibility and recruitment, are randomly allocated to receive one or other of the alternative treatments under investigation.

Specific for cohort studies

A cohort study is a form of longitudinal study (a type of observational study). A cohort is a group of people who share a common characteristic or experience within a defined period, e.g., are exposed to a drug or undergo a certain medical procedure. The comparison group may be the general population from which the cohort is drawn, or it may be another cohort of persons thought to have had little or no exposure to the procedures under investigation.

Frequent mistakes:

- Small samples sizes/groups investigated are combined with multiple outcome measures, resulting in weak data.
- Randomisation method(s) are poorly, or not, described.

2.2.2 Methods: Participants

The key issue is to select the appropriate patients[15] with the right type of wounds in the appropriate condition for the research question under investigation, bearing in mind that wounds may deteriorate over time due to the nature of the underlying disease. When more advanced therapies are used, these may intervene at the level of the patient's general health, making it important to report factors such as comorbidities.

For every study, you must define:

1. Eligibility criteria:

- Inclusion criteria: Who will be eligible to take part?

- Exclusion criteria: Who will be excluded from the investigation?

- Criteria and procedures for subject withdrawal or discontinuation.

2. Setting and locations for data collection

Where will the investigation take place (e.g. community or hospital?)

3. Number of patients and timelines

- The point of enrolment: when will they start in the investigation?

For more information about selection of subjects, please see:

15 ISO 14155: 2011 (Annex A)

For more information about frequent mistakes in study designs, please see:

1 Gottrup, F., Apelqvist, J., Price, P. 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.

Specific for RCTs

To access sufficiently large numbers of patients to make the data meaningful, multicentre trials are recommended. Efforts should be made to enrol sufficient numbers at each site used in the investigation in order to evaluate potential differences in outcomes across sites.

Specific for cohort studies

Although cohort studies allow you to follow a large group of patients, it is really important to ensure that you are collecting standardised data on each patient so that good comparisons can be made between those that receive different interventions.

Frequent mistakes:

- Power size: Studies often do not show statistical differences because the sample size is too small. Make sure you work with a statistician at the planning stage to work out how many patients you will need
- Patient characteristics are not predefined: this makes the interpretation of the data very difficult (you could make a type 1 or type 2 error; see section 2.2.5 on sample sizes for further information about error types).

- Expected duration of each subject's participation (time for participation in investigation)?
- Expected duration of the investigation
- Estimated time needed to select the required number of patients (i.e. enrolment period).

Each investigation site should maintain a log of all the subjects enrolled in the clinical investigation, assigning an identification code linked to their names, alternative subject identification or contact information.

2.2.3 Methods: Interventions

The interventions for each group must be described in sufficient detail to allow for replication of the investigation.[15]

The description of the interventions should include:

- Rationale behind intervention
- Details of the intervention
- The prognostic factors for the treatments groups
- Administration: How and when the interventions will be administered
- Treatment regimen: Number of treatment sessions, frequency and duration
- Other components of treatment: do the patients receive other treatments during the intervention?

Control/comparator interventions:

- Rationale for the control or comparator in the

For more information about the clinical investigation plan and selection of subjects, please see:

15 ISO 14155: 2011 (Annex A)

For more information about the various endpoints relevant for chronic wounds in general, please see:

1 Gottrup, F., Apelqvist, J., Price, P. 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.

For a detailed list on relevant endpoints and measurement methodologies in compression device studies, please see:

17 Rabe, E., Partsch, H., Junger, M., et al. Guidelines for clinical studies with compression devices in patients with venous disorders of the lower limb. Eur J Vasc Endovasc Surg 2008; 35: 4, 494–500.

context of the research question

- Precise description of the control or comparator
- Setting and context of the intervention, including instructions for clinicians
- Background/qualifications of the responsible clinicians

It is very important that the groups are comparable with regards to the nature of expected outcome for the intervention and identified prognostic factors.

Specific for cohort studies

If the cohort studies take place over a long period of time it is important to ensure that the setting and context of the intervention does not change significantly and that instructions are given to newly involved clinicians.

Frequent mistakes:

- Lack of comparable baselines for patient groups. E.g. standard care is not sufficiently described.

2.2.4 Methods: Outcome measures

Clearly defined primary and secondary outcome measure(s) and, when applicable, any methods used to enhance the quality of measurements (e.g. multiple observations, training of assessors) should be clearly predefined and reported, and related to the intervention. For example, if the research question focuses on infection, then resolution of infection may be a suitable outcome measure.[1]

Recommendations from the FDA support the view that complete closure of a chronic wound is one of the most clinically meaningful endpoints when referring to wound healing.[16] This is defined as skin re-epithelialisation without drainage or dressing requirements confirmed at two consecutive study visits two weeks apart. Other definitions of healing include rate of healing over time or time to complete healing. While complete healing may be the primary outcome under investigation, other types of clinically relevant outcomes should be incorporated depending on the intended purpose of the intervention in question. The important factor is to predefine your outcome measure and ensure you use the most objective way to measure that outcome.

Specific endpoints of interest in venous leg ulcer studies may be vein diameter, venous compliance, lymphatic drainage, leg volume, microcirculation, treatment effects (e.g. sclerotherapy, laser, or venous surgery), re-canalisation of a vein, lipodermatosclerotic skin changes and ulcer healing (See table 1 for further information about methods related to these endpoints).[17] However, some of these outcome may be difficult to achieve.

Specific for RCTs

Given the need for multicentre trials to recruit large samples, the training of assessors is important to ensure that everyone uses the same robust and reproducible measurement technique. Use blinded assessment wherever possible (See chapter 2.2.7 on blinding).

Specific for cohort studies

Often, cohort studies take place over a long period of time. In this case it is important that new staff who work at the centre are trained to ensure that predefined data are captured consistently over time.

Frequent mistakes:

- The primary outcome measure selected is not appropriate for the intended purpose of the intervention.
- The outcome measure is not predefined or is insufficiently defined.
- The outcome measures are not measured by a blinded assessor.
- Photos are not comparable or are not analysed correctly.

Table 1:VLU Parameters and methods[17]

Endpoint	Methodology
Vein diameter	ultrasound, phlebography
Venous compliance	pressure/volume relationship using simultaneous measurements of venous pressure and of volume lymphoscintigraphy, fluorescence microlymphoangiography, indirect x-ray lymphography, intralymphatic pressure measurement
Lymphatic drainage	water displacement volumetry, ultrasound, optoelectonic instruments, computerised digital photography, other validated methods
Leg volume	laser Doppler fluxmetry (to assess the veno-arteriolar reflex and vasomotor activity), transcutaneous oxygen tension, capillaroscopy, skin biopsy
Microcirculation Treatment effects, e.g. sclerotherapy, laser or venous surgery	efficacy parameters, effects on the frequency of side effects like phlebitis, pigmentation, bruising, pain etc. duplex, measurement of outflow fraction by strain gauge or air plethysmography (APG), quantitative assessment of refluxes by measuring venous filling index (ml/sec using APG skin thickness with high frequency ultrasound (e.g. 20 MHz), CT, NMR, by the durometer, tissue compliance monitor[18,19]
Recanalisation of a vein Lipodermatosclerotic skin changes	incidence of complete healing, area-planimetry, area in cm^2_p/4 (ellipse), Gillman method healing rate per unit time with correction for ulcer size (Ab_Aa)/(Pa þPb)/2) (b_a) [A: area of ulcer, P: perimeter, a: start and b: end of the observation], time to complete healing, life table analysis (should include all patients, including those lost to follow up) and treatment failures.[20]
Ulcer healing	symptoms on analogue scale including pain, CEAP, classification and VSS, QoL

2.2.5 Methods: Sample size

The sample size for a trial needs a good balance between medical and statistical considerations. Ideally, an investigation should be large enough to have a high probability (power) to detect a clinically important difference of a given size. Large samples are necessary to detect small differences.[3]

Elements of the sample size calculation include:

- the estimated outcomes in each group (which implies the clinically important target difference between the intervention groups);
- the type I (α) error level (i.e., false positive error; see Appendix 4);
- the statistical power or the type II (β) error level (i.e., false negative error; see Appendix 4);
- for continuous outcomes, the standard deviation of the measurements.

However, many areas of investigation, such as wound healing, do not have sufficient preliminary data on which to base these calculations.[1] Therefore, it is essential to obtain routine clinical data on the impact of care before initiating an investigation.

Within wound management studies, you may need to consider using a stratified sampling method. This method of sampling produces characteristics in the sample that are proportional to the overall population of patients with a given wound type, particularly where this is known to influence healing (for example, the size of the wound).

It is important to indicate how the sample size was determined. A formal power calculation should be used whenever possible; the authors

should identify the primary outcome on which the calculation was based, the values used in the calculation, and the resulting target sample size per study group.

Details should be given of any allowance made for attrition or non-compliance during the investigation and expected drop out rates should be defined. In addition, criteria for ending the clinical investigation on statistical or ethical grounds should be defined. To ensure that this is done correctly, please make use of specialist statistical advice.

For more information about sample size definition, please see:

3 Moher, D., Hopewell, S., Schulz, K.F., et al. Consort 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials; BMJ 2010; 340: c869.

Specific for RCTs

Recruiting a sufficiently large sample size is often a significant problem in the wound healing studies as most wounds are not directly comparable and the majority of patients are old and fragile, and suffer from diseases which may influence wound healing rates

Specific for cohort studies

Cohort studies may be considered a preferable study type within the wound area due to the problem with achieving a sufficient sample size.

Frequent mistakes:

- The intended sample size is not described in sufficient detail in the methods section of the trial publication.
- The trial is under-powered (i.e., an insufficient sample size was recruited to achieve statistically significant results).

2.2.6 Methods: Randomisation

The key distinguishing feature of an RCT is that study subjects, after assessment of eligibility and recruitment, but before the intervention to be studied begins, are randomly allocated to receive one or other of the alternative treatments under investigation. This is the central principle for high quality evidence required to demonstrate a possible causal relationship.[18]

With random allocation, each participant has a known probability of receiving each intervention before one is assigned, but the assigned intervention is determined by a chance process and cannot be predicted.

In designing your investigation, you will need a randomisation procedure to generate an unpredictable sequence of allocations, such as a simple random assignment of patients to any of the groups at equal probabilities. You will also need to think about allocation concealment, which refers to the strict precautions taken to ensure that the assignment of patients to a particular group/ intervention are not revealed prior to definitively allocating them to their respective group.

Authors should provide sufficient information so that the reader can assess the methods used to generate the random allocation sequence and the likelihood of bias assigning a patient to a particular group. This should include a description of:

- The method used to generate the random allocation sequence, including details of any restrictions (e.g. blocking, stratification)
- The method used to implement the random allocation sequence, clarifying whether the sequence was concealed until the interventions were assigned (to avoid bias).

- Who generated the allocation sequence, who enrolled the participants, and who assigned participants to their group?

There are no specific issues for trials in wound care that are different to studies in other health conditions and essential details should be reported. Although there is still debate on the appropriate variables that should be used for stratification, most commonly they are ulcer size and duration.

Given the need for an increased use of multicenter trials, the question of stratification by centre should be considered.

Important terminology:

- Simple randomisation: Pure randomisation based on a single allocation ratio.
- Restricted randomisation: Any randomisation not defined as simple (e.g. blocked)
- Blocked randomisation: Used to ensure balance of the numbers in each group
- Stratified randomisation: Used to ensure good balance of participant characteristics in each group.
- Minimisation: Ensures balance between intervention groups for several patient factors (e.g. age)

Suggested reading for more information on levels of evidence:

18 Burns, P.B., Rihrich, R.J., Chung, K.C. The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg 2011; 128: 1, 305–331

Frequent mistakes:

- "Random" is often used inappropriately in the literature to describe trials in which non-random, deterministic allocation methods were used, such as alternation, hospital numbers, or date of birth. When investigators use such non-random methods, these must be described precisely.
- It is important that information on the process of randomisation is included in the body of the main article and not as a separate supplementary file, where it can be missed by the reader.

Specific for RCTs

Main steps in a typical randomisation process:[3]

- Sequence generation: Generate allocation sequence using a random procedure
- Allocation concealment: Develop allocation concealment mechanism (such as numbered, identical bottles or sequentially numbered, sealed envelopes) and prepare the allocation concealment mechanism using the allocation sequence from the sequence generation step.
- Implementation: Enrol participants (assess eligibility, discuss the trial, obtain informed consent, enrol participants in the trial), ascertain intervention assignment (e.g., opening next envelope or use a central computerised service) and administer intervention.

2.2.7 Methods: Blinding (masking)

Blinding is a procedure that prevents study participants, their caregivers, or outcome assessors from knowing which intervention was received. Blinding is important because participants, healthcare providers, data collectors as well as data analysts can potentially introduce bias into a trial through knowledge of the treatment assignments.[3]

Participants may respond differently if they are aware of their treatment assignment (such as responding more favorably when they receive the new treatment). Lack of blinding may also influence compliance with the intervention, use of co-interventions, and the risk of withdrawing from the trial. Non-blinded healthcare providers may introduce similar biases, and non-blinded data collectors may differentially assess outcomes (such

as frequency or timing), repeat measurements of abnormal findings, or provide encouragement during performance testing. Non-blinded outcome adjudicators may differentially assess subjective outcomes, and non-blinded data analysts may introduce bias through the choice of analytical strategies, such as the selection of favourable time points or outcomes, and by decisions to remove patients from the analyses.

For more information about blinding, please see:

3 Moher, D., Hopewell, S., Schulz, K.F., et al. Consort 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials; BMJ 2010; 340: c869.

For specific considerations on wound care and blinding, please see:

1 Gottrup, F., Apelqvist, J., Price, P. 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.

Specific for RCTs

Often, terms such as single or double blind are used. This should be avoided wherever possible as there is great variability in the clinician interpretation and textbook definitions of these terms.

Suggestion for handling blinding within wound care studies:

If possible, make sure dressings have a similar appearance and let one assessor provide the care, while another person assesses the wound and a third person assesses the photo planimetry.

Frequent mistakes:

- No reports on whether and how blinding was used
- Blinding is not used for all relevant groups and there are no descriptions of how this may influence the results (risk of bias).
- If full blinding is not possible, the minimum requirement is a blinded assessment technique or an independent evaluation.

Blinding is particularly important when outcome measures involve some subjectivity, such as assessment of pain.

Many studies in wound care are open studies as the nature of the intervention often makes blinding complicated.[1] This increases the importance of using a blinded assessment technique that is as objective as possible in order to maximise the chances of reproducible findings. Observer/assessor blinding is the minimum requirement as this should always be possible to arrange, however, researchers should strive for the maximum blinding possible. Some areas are easy to blind, (e.g. topical treatments), while others are more difficult (e.g. dressings).

The blinding status of relevant staff/caregivers involved in the investigation should always be explicitly reported. At times, one group of individuals (such as the healthcare providers) are the same individuals fulfilling another role in a trial (such as data collectors). Even if this is the case, the authors should explicitly state the blinding status of these groups to allow readers to judge the internal validity of the trial.

2.2.8 Methods: Statistical methods

It is essential to specify which statistical procedure will be used to compare groups for the primary outcome.[3,15] If additional analyses are conducted, such as subgroup analyses and adjusted analyses, a full specification of these must be included in the study report. A subgroup analysis may, for example, be to look for evidence of a difference in treatment effect between complementary subgroups such as older and younger participants. Adjusted analysis may refer to controlling an imbalance in important participant baseline characteristics as part of multiple regression analysis.

The overall principle to follow is to, "Describe statistical methods with enough detail to enable a knowledgea-ble reader with access to the original data to verify the reported results" (www.icmje.org). It is also important to specify in an RCT whether the statistical analysis will be performed using intention to treat analysis (see box below for further information).

Almost all methods of analysis yield an estimate of the treatment effect, shown as a contrast between the out-comes in the comparison groups. Authors should provide a Confidence Interval (CI) for the estimated effect, which indicates a central range of uncertainty for the true treatment effect. The CI may be interpreted as the range of values for the treatment effect that is compatible with the observed data. It is customary to present a 95% CI, which gives the range expected to include the true value in 95 of 100 similar studies.

Study findings can also be assessed in terms of their statistical significance. The 'p' value represents the probability that the observed data (or a more extreme result) could have arisen by chance when the interventions did not truly differ. Actual 'p' values (for example, p=0.003) are strongly preferable to imprecise threshold re-ports such as p<0.05.

It is really important to make sure you get appropriate help and guidance from a statistician at the planning stage, and not once the data has already been collected.

For more information about statistical methods for RCTs, please see:

3 Moher, D., Hopewell, S., Schulz, K.F., et al. Consort 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials; BMJ 2010; 340: c869.

For a list of statistical considerations related to preparing the clinical investigation plan, please see:

15 ISO 14155: 2011 (Annex A, A7)

Specific for RCTs and clinical cohort studies

Intention-to-treat analysis refers to preserving the full benefit of the randomisation by including all randomised participants according to their group allocation. However, this is often difficult to achieve due to missing outcomes from some participants and non-adherence to the original protocol (e.g., when some participants did not meet the inclusion criteria or received a proscribed intervention).

A "per-protocol analysis" may be used in conjunction with the intention-to-treat analysis. The per-protocol analysis is a comparison of treatment groups that includes only those patients who completed the treatment originally allocated.

Frequent mistakes:

- Statistical procedures used are not thoroughly described.
- Multiple observations from one participant are treated as independent data. This is a serious error.
- Post-hoc subgroup analysis (performed after looking at the data) is used. This has a low credibility and should be avoided.
- Avoid common ways to boost samples, e.g.:
  - Different wounds on the same patients are placed in different groups
  - Two centres are involved, but 90% come from one of the centres (balance required).

2.3 Organisation and management

Securing a systematic management of the trial is important to ensure that the results comprise an adequate and useful contribution to the knowledge base within a specific area. Initial planning documents must include a plan for management of the patients, involved centres as

well as the study procedures and responsibilities of all involved persons. This will depend on the type of investigation, but all study designs require, as a minimum, a protocol defining exact timing and responsibilities for all actions needed to perform the investigation.

2.3.1 Important documents to ensure proper study management

The following documents are essential for securing that all regulatory and safety issues related to the investigation are met and that all aspects of the investigation have been considered and planned sufficiently to secure adequate results:[15]

- Study protocol or Clinical Investigation Plan (CIP): Includes information about the sponsor, investigators[14] and investigation sites and patient population (including inclusion/exclusion criteria, etc.); and state(s) the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation. Furthermore, the legal requirements by the national authorities as well as of the Ethical Committees of each involved country must be considered and reported (see suggested content in Appendix 1).

- Investigator's Brochure (IB):[15] Contains safety and performance data from pre-clinical and clinical investigations to compile the risk-benefit ratio of the clinical investigation and investigational device.

- Patient information sheet and consent form:[15, 19] Used to inform and obtain consent from patients concerning the use of their anonymised data; patients must be fully informed about the details of the investigation as well as the potential benefits and risks associated with participation. Patients must be made aware that they can withdraw from the study at any time without any explanation or detriment to their ongoing clinical care.

- Severe adverse event reporting form (SAE):[15] For medical device trials you should take a look at methods to classify adverse events related to devic-es in particular.[20] These may be classified as 'non medical complaint', adverse event (AE), serious adverse event (SAE), adverse device effect (ADE), serious adverse device effect (SADE), or unanticipated serious adverse device effect (USADE).

- Study contracts with the centres and all relevant staff.

For responsibilities of the study investigators and planning document examples, please see:

15 ISO 14155:2011(E)

For detailed information about patient information sheet and the Informed Consent Form (ICF), please see:

19 Consent Guidance and Forms - Guidance for Researchers & Reviewers; NHS. Available at: http://www.nres.nhs.uk/applica-tions/guidance/consent-guidance-and-forms/?1311929_entryid62=67013

For more information about adverse events, please see:

15 ISO 14155:2011(E)

For a paper on adverse event classification:

20 Stark, N. A New Standard for Medical Device Adverse Event Classification. J Clin Best Pract 2009; 5: 12.

2.3.2 Ethical and regulatory aspects of planning

Ethical and regulatory aspects of the investigation must be clarified and described prior to the investigation.[6,7,9,21]

Most clinical investigations have a sponsor that takes liability for the investigation. The sponsor may be an organisation such as a university, a company or a hospital, or an individual who may also be the principal investigator. Sponsors as well as investigators must avoid any influence on subjects or monitors taking part in the investigation.

Informed consent must be obtained in writing from all participants. This is crucial for obtaining approval from the ethical committee. Included information about the patient must be completed by an appropriately qualified physician or healthcare practitioner. Typically, a form including information and informed consent signature is produced. Any conflict of interest in relation to study investigators or other involved persons must be declared according to EU regulations.

For more information about the ethical principles and good clinical practice, please see:

6 ICH E6 (R1) Guideline for Good Clinical Practice. Available at: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html
7 WMA Declaration of Helsinki – for medical research involving human subjects: Available at: www.wma.net/en/30publications/10policies/b3/
9 EU Directive 2001: Good clinical practice in the conduct of clinical trials
Available at: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf
21 The National Health Authority or Medicines and Healthcare Products Regulatory Agency, e.g. UK: www.mhra.gov.uk

A list of documents to be provided to the Ethics Committee can be found in the ISO 14155:2011 document.[15]

2.3.3 Risk management & adverse events

Before initiating the investigation, the potential risks for involved participants should be evaluated. Once these have been identified, all involved investigators should receive relevant information/education needed to reduce the risk of injury (e.g. at an investigator meeting prior to the start of the clinical investigation). The risk analysis must include the identification and characterisation (nature, incidence, severity and outcome) of anticipated adverse events related to the use of a medical device. This information must be included in the Investigator's Brochure[15] as well as the Informed Consent Form[19] to be signed by participants prior to enrolment.

It should also be clear how potential injury claims should be reported and evaluated; methods of compensation should be outlined, should a claim be evaluated as valid. In the case of a (serious) adverse events, it is the responsibility of the investigator to provide adequate medical care to all those involved during and after participation in the investigation, and to inform the participants of the nature and possible cause of any adverse events experienced.

Prior to the investigation, all subjects must be informed about the well-defined procedures for emergency situations related to the investigation and necessary arrangements must be made for possible emergency treatment. Any adverse event must be reported to the study sponsor and detailed information must be included in the Clinical Investigation Plan (CIP). In case of serious adverse events these must be reported

to regulatory authorities in accordance with national regulations. The progress of the clinical investigation, the safety data and/or the critical performance endpoints must be assessed with regular intervals. Based on this, recommendations must be given to the sponsor on whether to continue, suspend, modify or stop the clinical investiga-tion. An independent committee such as the data monitoring committee (DMC) should be established by the investigator/sponsor; e.g., depending on the risks for the patients involved in the clinical investigation.

2.3.4 Centres & study personnel – qualifications

The study sponsor is responsible for defining the roles and responsibilities related to the clinical investigation, selecting qualified centres, a coordinating investigator and appointing monitors. In multi-centre studies, a lead investigator must be appointed at each involved centre/site in addition to the principal investigator who is responsible for the overall investigation. If several countries are involved in the investigation, a principal investigator for each country may be needed due to the national regulations.[15] The principal investigator must have previous experience with using the device as well as knowledge about the relevant regulations. To ensure that Principal Investigators have a sufficient level of knowledge of the relevant regulations, it is important to take a look at the National Regulatory Agency.

The lead investigator in each centre/site is responsible for demonstrating that the centre has the required number of eligible subjects needed for the investigation and that the centre has the adequate facilities and a qualified investigation team to run the study. All roles and responsibilities must be described and formally agreed in writing.

The sponsor is also responsible for recording the level of knowledge and experience of centres and investigators involved in the study, and for providing training if necessary/required.

A possible layout for recording all relevant employees at a study centre can be found in Appendix 2.

For more information about the responsibilities of the principal investigator appointed in the involved centres, please see:
15 ISO14155:2011 (E), p. 28: 9

2.3.5 Contract research organisation (CRO)

The CRO may be a person or organisation contracted by the sponsor to perform one or more of the sponsor's clinical investigation-related duties and functions. These functions should be summarised in a contract.

2.3.6 Patients/participants enrolment

Important documents related to the subjects/participants in the study are:

- A recruitment status sheet/subject identification log which presents an overview of and status on the subjects registered for the investigation. An identification code should be assigned to all subjects.
- An informed consent form, approved by the relevant ethical panel/committee: all subjects who agree to participate in the investigation must sign this prior to any involvement

(See chapter on risk management for further information).

- Case Report Form (CRF): this document must capture all the relevant data for each enrolled subject. All subject data must be kept strictly confidential and in line with the country-specific data protection legislation.

- Monitoring plan: This plan must enable the sponsor to assess the extent and nature of monitoring appropriately for the clinical investigation, including the strategy for source data verification. Monitoring time points should relate to the design, complexity, size, critical data collection points and the primary endpoints of the clinical investigation.

An example of a combined recruitment/ monitoring form can be found in appendix 3.

Clear inclusion and exclusion criteria must be defined for recruitment purposes. You can find a set of criteria examples in Table 2.

An estimation of expected withdrawal rate/drop out rate should be performed prior to the initiation of the study (e.g. based on results from other published clinical investigations on comparable therapies). You can find an example of possible withdrawal criteria in Table 3.

Table 2: Side effects– General inclusion and exclusion criteria

Criteria	Ulcus cruris venosum
Inclusion criteria	•Exact diagnosis based on CEAP classification (C6)[22] •Signed "Informed Consent" of the patient •Patients of both sexes •Wound size: leg ulcers from 2–100cm^2 •Receiving compression therapy for at least 2 weeks before inclusion •Age between 20–80 years
Exclusion criteria	•Severe arterial disease •Asymptomatic and symptomatic peripheral occlusive arterial disease, malleolar artery pressure values with a reduced ankle/arm index (<0.8, if not part of the study design) •Immobile patient/bedridden patient (if not part of the study design) •Insulin-dependent diabetes mellitus •Cytostatic or immunosuppressive drugs •Allergy against one of the used materials •Pregnancy and period of lactation •Under 20 years old or over 80 years old

Table 3: Examples of withdrawal criteria

Criteria	Ulcus cruris venosum
Withdrawal	•Deterioration in the clinical picture of the disease, if not indicated in the designed study population •Clinical deterioration (continued participation is no longer in the best interest of the patient) •The condition of the wound •Lack of concordance by the patient •Withdrawal of patient consent (this has to be documented) •Change in measures and events that affect the target criteria (example: initiation, change or discontinuation of hormone therapy, diuretic treatment) •Intercurrent infections (if not part of the study design)

2.3.7 Clinical sample logistics

Labelling of the clinical samples depends on national regulations. Most often the labels must include all information included on the label for the certified product (e.g. name of the product (if not blinded), name and address of the manufacturer, storage conditions, sterilisation method, and expiry date). Furthermore, you should add a label indicating that this is a "clinical investigation sample". For non-blinded clinical investigations using certified products with instructions for use, an additional marking is not necessary if the study is not randomised.

A table including information about the samples sent to each centre should be produced. In each centre, the lead investigator must ensure that the samples are only used for the clinical investigation and carefully stored (locked storage conditions).

2.3.8 Financial plan

The sponsor needs to ensure that a financial plan is developed for the clinical investigation.[6] The financial budget must guarantee that the clinical investigation can be performed and include a plan for loss of the study sponsors (e.g. due to insolvency) or early termination of the clinical investigation. Usually the financial budget will be evaluated by the Ethical Committee, as well as the responsible authority.

For more information about sponsor role and financing, please see:

6 European Medicines Agency, ICH topic E6 (R1): Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000072.jsp&mid=WC0b01ac05800268ad

Frequent mistakes:

A list of frequent mistakes related to study management is provided in Table 4

Specific for RCTs

Detailed instructions for the RCT must be written in the protocol and followed rigorously. The decisions of the Ethical Committee (pre- and post-market), and approvals from the responsible authorities should be included in the study file (especially for pre-market product trials).

Specific for cohort studies

- Study details must be written in the protocol and followed rigorously.
- The clinical data may be evaluated retrospectively or prospectively.
- The medical devices must be used according to their "instructions for use" (post-market study).

Table 4: Frequent mistakes related to study management (modified version of table in EWMA Document: Outcome in controlled and comparative studies on non-healing wounds, 2010)

•No contracts are prepared.
•The different tasks of various participants are not described (e.g. sponsor, principal investigator, clinical investigator, supporting clinical staff in the center)
•No financial plan is prepared.
•Study forms are incomplete.
•Informed consent form for patients is not clear.
•Missing ethical approval or approval by authorities.
•Parts of the investigators brochure are missing (e.g. biocompatibility, assessment of the benefit-risk of the clinical investigation).
•Statistical evaluation is not fit for purpose (e.g. low study power, references analysis patterns in other studies are missing).
•Monitoring/auditing is not sufficient (e.g. too many open queries, no correct adaptions in the CRFs by investigators, informed consent form is not signed by the patient or the patient was not properly informed by a physician).
•Reporting of (serious) adverse events is insufficient (no timely reports from clinical investigators/sponsors, bad coordination, no presentation of corrective actions when needed).
•Clinical investigators have no experience with medical device studies and the related regulations.
•Incorrect selection of the comparison group (definition of standard care missing).
•Recruitment of patients in each centre is insufficient within the defined time frame.
•No validation of subjective assessment.
•No description of objective or subjective measurement techniques.
•No comparable baseline for patient groups.
•No blinding in the evaluation of primary outcomes.
•Incorrect randomisation methods.
•Poor definition of primary and secondary objectives/outcome measures
•Patient numbers are not based on a prior sample size calculation.
•Randomisation method poorly/not described.
•Assessment of outcome measures not fully objective.
•'Intention-to-treat' analysis is not used.
•Heterogeneous study populations.
•Number of and reasons for dropouts are not stated.
•No specification of adjuvant treatments.
•Small sample size combined with multiple outcome measures.
•Reporting of multiple outcomes over several time periods (increases occurrence of type I errors).

Chapter 3: Data collection

3.1 Inclusion, monitoring and quality assurance

It is important that you select patients according to the clinical investigation plan, which should provide clear exclusion/inclusion criteria (see chapters 2 and 3). Appendix 3 shows an example of a recruitment & monitoring form.

It is good practice to appoint a committee of independent clinical and statistical experts to review study data on one or more planned occasions while the investigation is ongoing. After each data review meeting, the monitoring committees will make recommendations to the sponsor or investigation steering group, that are also reported to institutional review/ethics boards. For example, the data monitoring committee can recommend protocol amendments, additional study procedures to assess safety or efficacy, or early termination of an investigation for reasons of safety or efficacy.

Data collection must reflect the study protocol content and be unambiguous in the sense that they provide the information needed to answer the questions defined in the protocol (See chapter 2.2 methods).

The overall responsibility for the quality assurance of the study lies with the study sponsor.

For quality assurance measures and quality control in the data collection the following actions must be taken:

- Maintain written quality procedures to ensure that data are generated, documented and recorded in compliance with international standards (e.g., ISO 1415515).
- Maintain records to document the compliance of all parties involved in the investigation (see chapter 2.3.1).

Table 5: Selection bias and performance bias

	Accepted Practice	Application to Wound Management
Selection bias (All eligible patients should have the same chance of receiving the intervention. Both groups are similar at baseline)	Random allocation, concealed allocation	There are no particular issues for wound management studies, and all efforts should be made to randomly allocate patients to groups.
Performance bias (All patients should receive exactly the same treatment with the exception of the study intervention)	Participants are blinded to treatment allocation. Clinicians (who administer an intervention) are blinded to treatment allocation	The details of standard treatments should be made explicit. It may be difficult to achieve, but the highest level of blinding should be used within an RCT. Double blind studies are often difficult but blinded (or independent) assessment of outcome/ endpoint should be mandatory (especially if the study is not blinded). Blinded analysis of data should be easy to undertake..

For more information about bias, please see:

1 Gottrup, F., Apelqvist, J., Price, P. 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.

For more information about quality procedures, please see:

15 ISO14155:2011

3.2 Minimum dataset

In order to increase the potential for studies to be compared robustly, or be collated into a meta-analysis, it is important that we start to develop agreed elements in the datasets that are collected within studies. A minimum dataset[23] provides a list of items and definitions necessary for data collection aimed at creating useful patient data records. It is crucial that parameters that are known to have effect on the condition in questions (in our case, wounds) are included in the minimum dataset.

With regards to standardising the collection of data within the field of wound management research, it is important that clinicians across countries and treatment settings use a set of minimum core data when conducting research within the field. Standardised data will enable clinicians to compare data across populations, settings, geographical areas and time.

Currently, there is no standard use of minimum dataset within wound management research. EWMA considers this is an important next step to secure more comparable data in wound research. This would also meet the requests for more cross European data on best practice treatment methods and health economical aspects.

The suggested dataset listed in table 6 includes our proposals for the information you need to provide about the patient to give the basis for your evaluation of the outcome of the product or treatment method in question.

These are based on an evaluation of the key issues that we know affect the outcome of venous leg ulcers and should be taken into consideration when defining the outcome measures of the study. These could be factors influencing the generalisability of the data.

For general information regarding minimum dataset, see for example:

23 Werley, H.H., Devine, E.C., Zorn, C.R., et al. The Nursing Minimum Data Set: abstraction tool for standardised, comparable, essential data. Am J Public Health 1991; 81: 4, 421–426.

Table 6: Common set of variables for reporting on chronic wound studies: Leg ulcers

	Domains / Variables
1	Sociodemographic Data
1.1	Age (Numerical, years)*
1.2	Sex (1=m, 2=m)
1.3	Socioeconomic status
1.4	Professional status
Add if relevant:	Housing status, insurance payer status, geographic area/region
2	General health
2.1	Weight (Numerical, kg)*
2.2	Height (Numerical, cm)*
2.3	BMI (formula, kg/cm^2)
2.4	Comorbidity
2.5	Co-medication
2.6	Nutrition status
2.7	Vascular status: ABPI
2.8	Vascular status: Venous insufficiency
3	Wound history
3.1	Wound location
3.2	Wound aetiology
3.3	Duration of wound disease (Numerical, mth/yrs)*
3.4	Duration of target wound (Numerical, mth/yrs)*
4	Wound condition & outcomes
4.1	Number of wounds (Numerical)*
4.2	Wound area/size of target wound (Numerical, cm^2/cm^x)*
4.3	Time to complete healing (Numerical, days/weeks)*
4.4	Granulation tissue formation (%) (Only if primary endpoint)
4.5	Healing rate (%)
Add if relevant:	Amputation rate (Numerical)*, Wound area: all wounds (Numerical, cm^2)*
5	Patient reported outcomes
5.1	Disease-specific quality of life (Numerical, global score)*
5.2	Pain (0-10 VAS) (Classify)
Add if relevant:	Generic quality of life (global score) Use screening instrument: e.g., WHO: http://www.who.int/mental_health/publications/whoqol/en/
6	Treatment
6.1	Further topical wound treatment
6.2	Additional treatments (e.g. compression)
6.3	Pain medication
6.4	Use of antibiotics (Systemic)
6.5	Debridement, surgical (Describe frequency)
Add if relevant:	Other treatments relevant to wound care
7	Healthcare/health economy
7.1	Healthcare providers
7.2	Resource utilisation (Define cost perspective)
7.3	Days off work (Numerical)*
7.4	Out-of-pocket-expenses (Numerical)* (Local currency or Euro)
7.5	Quality of healthcare (Use standard indicators)

*Numerical variables for analysis include Mean, SD, Median, Max, Min

The dataset is based on a proposal by Mathias Augustin, Prof., MD, Dept. of Dermatology, University Clinics of Hamburg

Chapter 4: Use of data

When analysing, interpreting and reporting the collected data, it is important to follow the initial plan for describing and assessing the data. If there is a need to deviate from the original plan, the reasons should be stated clearly.

In order to avoid bias, it is a good idea to separate data collection and the study conduct from the data analysis and reporting (i.e., these are undertaken by different staff).

In the following section, you will find some general and wound related advice on data management, analysis, interpretation, reporting and publication.

Please note that different rules apply to reporting to ethical committees in different countries.[24]

The European Network of Research Ethics Commit-tees (EUREC) provides links to national legislation:

24 www.eurecnet.org/index.html

For more information on data documentation, please see:

1 Gottrup, F., Apelqvist, J., Price, P. 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.
3 Moher, D., Hopewell, S., Schulz, K.F., et al. Consort 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials; BMJ 2010; 340: c869.

4.1 Data management

The following aspects of good data management are crucial for good study conduct and should always be followed to ensure that study quality and ethical standards are met.

4.1.1 Data documentation

All subjects enrolled in the clinical investigation (including those withdrawn or lost to follow up) should be accounted for and documented in order to prove that data was not invented and to avoid double entries. This is typically done by securing that patient data are signed and dated and may be handled by using a recruitment/monitoring form (see Appendix 3), or electronic database.[1,3,15]

Wound management studies often have high drop out rates due to the type of participants, and these details must be reported, including information about the reason for withdrawal. Using a run-in period to address the change in wound status can help to increase homogeneity of groups, and reduce drop-out rates. Studies should plan their recruitment to allow for potential withdrawals, especially when there are long intervention periods.

If such a withdrawal is due to problems related to the investigational device safety or performance, the investigator should ask for the subject's permission to follow his/her status/condition outside the clinical investigation.

To avoid attrition bias, the general/recommended

practice is to ensure that:

- All groups are followed-up at the same time;
- Rates of drop-out are not high in either group;
- Both groups should be similar in terms of patients remaining in the analysis (and similar to baseline).

4.1.2 Confidentiality

Everyone involved in the investigation, and at all times throughout the clinical investigation, must observe all requirements related to the confidentiality of patient data and study outcomes.

All data must be secured against unauthorised access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data.

4.1.3 Access to data

The principal investigator or institution shall provide direct access to source data during and after the clinical investigation for monitoring, audits, Ethical Committee (EC) review and regulatory authority inspections. It is also required that the principal investigator or institution obtains permission for direct access to source documents from the subject (informed consent is presupposed; see chapter 2.3.5), hospital administration and national regulatory authorities before starting the clinical investigation.

4.2 Analysis

Analyses, e.g. performance of a medical device such as a wound dressing, that were pre-specified in the trial protocol (prepared in the initial phase) should be used. If subgroup analyses were not pre defined, authors should report which subgroups were examined and include justification for these analyses.

You should therefore report which analyses were pre-specified and make the trial protocol available so that interested readers may access this to find information.

For company-sponsored research or if you wish to publish the results of your research in highly recognised journals, it is mandatory that the study is registered in a public database (e.g. www.clinicaltrials.gov[25]) before the investigation begins. You should therefore consider this requirement in advance.

In general, it is recommended that the following information is included in the analysis:[1,3,13,15]

- Performance and safety assessment:
  - Identify datasets that are considered most important in contributing to the demonstration of the overall performance.
  - Provide a summary of all adverse events and adverse device events, including a discussion of the severity, treatment needed, resolution and relevant principal investigator's judgment concerning the causal relationship with the investigational devices or procedure;
  - Provide a table compiling all observed device deficiencies that could have led to a serious adverse device effect, and any possible corrective actions taken during the clinical investigation.
- Pre-planned subgroup analyses for special populations (i.e. gender, racial/cultural/ethnic

25 **www.clinicaltrials.gov** is an official platform and catalogue for registering a clinical trail. ClinicalTrials.gov, run by the United States National Library of Medicine (NLM), was the first online registry for clinical trials and is the largest and most widely used internationally today.

subgroups), as appropriate;

- An account of all subjects with a description of how missing data or deviation(s) were dealt with in the analysis, including subjects not passing screening tests, lost to follow-up, withdrawn or discon-tinued from the clinical investigation and the associated reasons (see data management).

4.3 Interpretation

The interpretation of data should identify meaningful clinical observations and report the clinical meaning and relevance of outcomes. As a result of good initial planning and the appropriate definition of the primary outcome measures, the results should be interpretable within the size of the sample selected for inclusion in the study.

To avoid detection bias, the interpretation must be based on the initial planning of the investigation as outlined in the box.

As previously mentioned, blinding may be a challenge in wound studies, but this recommendation should be met whenever possible (See in chapter 2.2.7 methods: blinding).

In order to make generalisations about the findings, issues with regards to external validity and applicability of the findings should be considered. These considerations should be made in the planning phase, as the data collection must support these aspects of the interpretation (e.g., the risk of a healthy selection bias may compromise the validity of generalised results).

To ensure that high quality and appropriate analysis takes place, it is always recommended to involve an experienced statistician from an early stage in the design of the investigation. When the study results are likely to be used by regulatory bodies, a qualified biostatistician must be included as one of the investigators, otherwise the data may not be accepted for review (see chapter 2.2 Methods).

Whenever possible, develop a statistical analysis plan (SAP). The SAP is a plan for analysing study results. It is written by statisticians and approved by regulators prior to study conclusion.

For more information about analysis of data and reporting, please see:

1 Gottrup, F., Apelqvist, J., Price, P. 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.
3 Moher, D., Hopewell, S., Schulz, K.F., et al. Consort 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials; BMJ 2010; 340: c869.
13 MEDDEV 2.7.1 Rev. 3, Guidelines on Medical Devices, Clinical Evaluation: A Guide for Manufacturers and Notified Bodies, Dec 2009
15 ISO 14155: 2011

Limitations:

- Remember to discuss the relevant limitations of the study that were not anticipated as part of the interpretation of data. A discussion about the reason(s) for unforeseen limitations and what they may tell us about the outcome measures in question may be a relevant and a useful part of the interpretation of findings, which should not be ignored.

To avoid detection bias:

- Provide a precise definition of outcome including adequate follow-up periods allowing for recurrence rates;
- Define a valid and reliable method to measure outcome (the outcome measure should be objectively measurable and repeatable);
- Ensure an appropriate length of follow up which is adequate to identify outcomes;
- Make sure investigators (responsible for assessing outcomes) are blinded to initial treatment allocation;
- Make sure investigators are blinded to other important confounding or prognostic factors

Read the SAP, but don't be too concerned about comprehending statistical minutia.

4.4 Content: Report and scientific article

Study reports are intended to give a comprehensive picture of the research process and findings while a scientific article submitted for publication in a journal may focus on specific parts of the study and will need to keep the interest of the readers, e.g. by keeping information concise. This can be difficult to achieve, given the paper must include sufficient detail to allow for a critical review. Thus, the intended audience as well as the content differs in these two types of research publications.

The following questions are central when you evaluate your audience: What is their level of knowledge, what are their interests, why would they read the report or paper (e.g. product evaluation or interest in topic) and should the text be short and concise or a longer, in-depth description of specific findings?

4.4.1 Report

When reporting to a local or international authority, the information included should be detailed and comprise all findings relevant for a thorough evaluation of the product or treatment method in question.

For a detailed suggestion for content of the clinical evaluation report, please see:

13 MEDDEV 2.7.1 Rev. 3, Guidelines on Medical Devices, Clinical Evaluation: A Guide for Manufac-turers and Notified Bodies, Dec 2009
(Appendix E: A Possible Format for Clinical Evaluation Report)
15 ISO 14155: 2011 (Provides a clear content outline)
Appendix F: Clinical evaluation checklist for Notified Bodies

The report content should include the following:[13, 15]

1. General details

- State all relevant details on name of product or treatment method.
- For products, include manufacturer details.
- Include name of the principal investigator/ coordinating investigator.
- State whether the investigation was conducted in accordance with international standards and applicable regulations.

2. Summary

Brief summary of the key report content, according to the purpose of the study.

3. Introduction

4. Description of the product/treatment method and its intended application

- State whether the product or treatment method is a new technology/method or new clinical application/the result of incremental change of an existing technology/method.
- Intended therapeutic and/or diagnostic indications and claims
- Describe essential requirements relevant to the product or treatment method (e.g. performance or safety).

5. Clinical investigation

- Context of the evaluation, outcome measures and choice of clinical data types.
- Ethical considerations and data quality assurance
- Sample size and inclusion/exclusion criteria

- Treatment allocation schedule
- Duration of follow up
- Statistical analysis including sample size calculations and methods

6. Results:

- Summary of the clinical data and appraisal
  - Include a table of the clinical data used in the evaluation (state whether the data addresses the performance or the safety of the product or treatment method in question).
- Data analysis
  - Performance: Provide a description of the analysis used to assess performance.
  - Safety:
    - Describe the total experience with the product or treatment method (including numbers and characteristics of patients exposed to the device; and duration of follow-up)
    - Give a summary of related adverse events, paying particular attention to serious adverse events.
    - State whether end user training is necessary.
  - Product literature and instructions for use: If you are evaluating a product, state whether the manufacturer's product literature and instructions for use are consistent with the clinical data.

7. Conclusions

- Outline clearly the conclusions reached about the safety and performance of the product or treatment method from the evaluation, with respect to the intended use.
- State whether the risks identified have been addressed by the clinical data.

For a detailed content outline of reporting in medical device trials, you should read the detailed information in ISO 14155: 2011 (Annex D).[15] This includes specific instructions on reporting ethical issues.

If relevant, a possible methodology for documenting the screening and selection of literature within a literature search report can be found in MEDDEV.[2.7.1.13]

4.4.2 Scientific articles

As a minimum, the study report and papers submitted for publication should include the following sections:

- Abstract: Background for the investigation, basic procedures, main findings and principal conclusions
- Introduction: Background for the investigation; why ask this research question?
- Methods: What did I do?
- Results: What did I find?
- Discussion: What might it mean? For example,
  - Considerations of possible mechanisms and explanations, including safety and performance results and assessment of risks and benefits.
  - Comparison with relevant findings from other published studies
  - Limitations of the present investigation (and methods used to minimise and compensate for those limitations).
  - A brief section summarising the clinical and research implications of the work, as

appropriate for the investigation in question.

You may also add a conclusion stating whether the study objectives were achieved and key messages from the study, depending on the style requirements of the journal.

The author(s) of the report are usually identified as those who have contributed intellectually to the study and the article, rather than data collectors (although these may be the same people). Authorship should be clarified in the initial stage of the study planning. Each author's highest academic degree should be listed. You should also remember contact information of the corresponding author as well as stating possible conflicts of interest of each author.

With regards to meeting the requirements for content and formalities of scientific papers, you should follow the recommendations of the International Committee of Medical Journal Editors.[26]

Before submitting a paper for publication in a scientific journal, you should check the journal's word limit and formats (including the preferred referencing style). When including tables and pictures, it is important that they have the right format and quality and that clear references are made in the text.

Within wound management, there is a general concern that a substantial number of studies on different wound intervention are not published or not available in indexed journals. However, all research results should undergo an independent peer review evaluation and be made available to the public, whether the outcome is positive or negative. This is important to avoid publication bias (see note on publication bias below).

For a full description of manuscript preparation, please see:

26 ICMJE, Preparing for Sub-mission. Available at: http://www.icmje.org/recommendations/browse/manuscript-preparation/preparing-for-submission.html#g

For more information about good medical writing and formalities:

27 Groves T, Fundamentals of good medical writing, BMJ Open. Available at: www.bmjopen.bmj.com/site/about/resources/Fundamentals_of_Good_Medical_Writing.ppt
28 International Committee of Medical Journal Editors http://www.icmje.org/manuscript_a.html

Publication bias

To avoid publication bias, it is important that negative results are reported. As noted under planning, it may be relevant to get a written agreement with the study principal investigator, before the investigations is initiated, about publication of negative data and data access after the study period

A concluding remark

This document aims to highlight key features you will need to think about when planning, conducting, analysing or reporting an RCT or cohort study. It is not a comprehensive guide to every aspect of the process, as there are already a substantial number of guidelines and recommendations in place, many of which we have mentioned along the way. Many of the existing recommendations for the conduct and reporting of trials apply equally to wound care studies as to any other health condition, so there is no need to 'reinvent the wheel'. However, we are all aware that the quality of many studies in this field remains poor and we would be doing a disservice as the European Wound Management Association if we did not encourage our members to join in the challenge of raising the quality of studies for the benefit of our patients.

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Appendix

Appendix 1: Study Synopsis Form for *in vitro*, *in vivo*, *ex vivo* and clinical investigations

Title	
Study Acronym	
(study number)	
Sponsor	
Investigator and Centres	Principal Clinical Investigator: Contact information Centres: Contact information
Centres: Contact information	
Aim of the study	
Indication (for clinical studies)	
Material / Methods used	
Study Design	
Clinical Phase	
Study population	
Ethical Committee / National regulations	According to the national law and Declaration of Helsinki proposal: The Principal Clinical Investigator takes responsibility in order to conduct the study with the appropriate documents (i.e. written consent form of the patient) as well as in accordance with the Helsinki Declaration II of 2000 and the ISO 14155: 2011 "Clinical investigation of medical devices for human subjects- Good Clinical Practice" and fulfill the national legal requirements. A signed "Informed Consent" of the patient must be available to integrate the patient into the study. For certified medical devices used in its "instructions for use". Ethical approval is not required as all used products are licensed, CE-certificated medical devices for wound management and are applied in its certified instructions for use as well as integrated in the usual therapeutical procedure of the centers.
Insurance for subjects	According to national law.
"Informed Consent" of the subjects (patients/volunteers)	A signed "Informed Consent" of the subject must be available to integrate the subject into the study.
Period of treatment	
Periods of dressing change	

Duration of the study	
Procedure of treatment	Visit-Plan
Primary Outcome	
Parameter (endpoint) for clinical studies	
Secondary Outcome Parameters (endpoints) for clinical studies	
Inclusion criteria	
Exclusion criteria	
Randomisation	
Withdrawals/dropouts	
Unexpected Adverse Events/Incidents according to the MDD	
Special procedures (e.g. compression)	
Statistics	Methods Hypotheses Interim evaluation
Documentation	Handling
Monitoring / Audit	Visits and audits by monitors or auditors

Appendix 2: Involved employees of the centre

Name	Title and Position	Task	Initials	Period (from – to)	Signature (main investigator of the center)

Task 1: Screening of patients; 2: Patient Informed Consent; 3 Medical examination; 4: Documentation with questionnaire (CRF); 5: Signature of the CRFs; 6: Others (please explain)

Appendix 3: Recruitment / Monitoring

Pat. Initials	Birth. Date	Patient Informed consent date/done by (physician)	Start of treatment date / done by	End of treatment date/ done by	Documentation during monitoring visit Query check (date/signed by monitor)	Documentation during monitoring visit Query check (date/signed by monitor)	Transfer of the final documentation to the monitor (date/signed by monitor)
Attention: the signed names have to be readable and integrated in the "list of involved persons".							

Appendix 4: Type I and Type II errors

Type I error, also known as a **"false positive"**: the error of rejecting a null hypothesis when it is actually true. In other words, this is the error of accepting an alternative hypothesis (the real hypothesis of interest) when the results can be attributed to chance. Plainly speaking, it occurs when we are observing a difference when in truth there is none (or more specifically - no statistically significant difference). So the probability of making a type I error in a test with rejection region R is P ($R|H_0$ is true).

Type II error , also known as a **"false negative"**: the error of not rejecting a null hypothesis when the alternative hypothesis is the true state of nature. In other words, this is the error of failing to accept an alternative hypothesis when you don't have adequate power. Plainly speaking, it occurs when we are failing to observe a difference when in truth there is one. So the probability of mak-ing a type II error in a test with rejection region R is **$1 - P(R|H_0$ is true**). The power of the test can be P($R \mid H_0$ is true).