A list of common methodological errors in wound-dressing trials

- Lack of validation of subjective assessments
- Lack of description of objective or subjective measures
- Lack of comparable baselines for patient groups
- Lack of blinding for the evaluation of primary outcomes
- Incorrect randomisation methods
- Poor definition of primary and secondary objectives
- Number of patients not based on a priori sample size calculation
- Randomization method poorly/not described
- Assessment of outcomes not completely objective
- Time to wound healing not used as primary outcome
- Intention-to-treat analysis not used
- No use of single reference wounds
- Heterogeneous study population
- Number of and reason for dropouts not stated
- No specification of adjuvant treatments (such as pressure-relieving surfaces or offloading devices for neuropathic ulcers)
- Small sample size combined with multiple outcome measures
- Reporting of multiple outcomes over multiple time points (increases chance of type I error)
- Poor overall study reporting

Key messages

- There is always a compromise between maintaining a purist approach and being pragmatic about the ways in which treatments are used in routine practice.
- Consistency in measuring endpoints /outcomes improves quality of data
- "Basic care" must be standardized
- The Patient Outcome Group supports the use of RCTs in wound management research but advocates clinical trials should use appropriate endpoints for the intervention under investigation.

For further information about the EWMA Patient Outcome Group, please visit www.ewma.org/english/patient-outcome-group

Any questions concerning EWMA Patient Outcome Group or the document can be sent to EWMA Secretariat: ewma@ewma.org

The EWMA Patient Outcome Group is supported by an unrestricted grant by:

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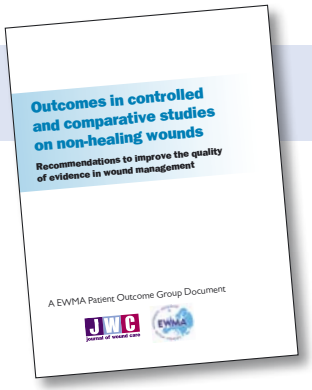
Outcomes in controlled and comparative studies on non-healing wounds

– recommendations to improve the quality of evidence in wound management



F. Gottrup, J. Apelqvist, P. Price. "Outcomes in controlled and comparative studies on non healing wounds – Recommendations to improve quality of evidence in wound management" Journal of Wound Care 19(6): 237-268 (Jun 2010)

The Patient Outcome Group is very thankful to Dr. Brigitte Espirac for writing this 'pixi' version of the POG document.

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The clinical perspective

The aim of this folder is to provide a brief summary of recommendations on:

- How to achieve rigorous endpoints/outcomes in studies on wound management
- An approach that will enable the design of Randomised Controlled Trials (RCTs) and clinical studies to be both consistent and reproducible in order to reach a higher quality of evidence in wound management.
- A framework for clinicians when conducting clinical studies or evaluating clinical data

The nature and extent of the problem for Wound Management

- Different types of evidence are available: e.g. meta-analyses, well-conducted RCTs
- Trials in wound management should, whenever possible, adhere to guidelines for conducting and reporting clinical studies
- In wound management there is a paucity of high-quality evidence, or observational data from high quality cohort studies
- The extended definition by Sackett (1996) may be more relevant in the wound sector. Sackett proposed that evidence-based medicine is not restricted to randomised trials and meta-analysis, but involves the exploration of all types of best external evidence. Prospective cohort studies may be particularly helpful, especially when cost and resource use are the major outcome of interest.

Key issues regarding the use of RCTs in wound management

- All individuals involved in conducting a RCT must be trained to ensure that each patient included follows the same protocol.
- Heterogeneity of the study population can cause problems
- In interventional studies, wounds may not only heal or improve but may also deteriorate which may impact on the attrition rate
- A purist approach to RCT design stipulates that a single intervention should be investigated until the primary outcome is achieved.

The clinical research perspective: Preliminary considerations

- Purpose of the study must be clear: clinical data, economic data, registry
- Study design must be as rigorous as possible
- Sample size and randomization must be adequate
- Statistical analysis must be described in the protocol (ITT and PP)
- Precise endpoints /objectives should be used
- Results include patient flow, recruitment, baseline data and management of adverse event

The most important element in establishing high quality evidence in wound management is the choice and definition of outcome parameters.

Standard measurement criteria are essential if results are to be accepted by the clinical community.

Definition of endpoint

- An endpoint is defined as *the objective of an evaluation or study.*
  The objectives should include:
  - A precise statement of the degree of benefit expected from the intervention and its duration
  - Clear statements on the time frame of the study (especially in relation to how quickly the benefits might start)
  - A definition of the patients for whom the benefit is sought
- Endpoints can be classified as either primary or secondary.
  - Primary endpoints provide the focus of the study.
  - Secondary endpoints allow for the investigation of subsidiary questions.

Possible Endpoints:

- *Wound closure* (total epithelialisation without discharge) is the most important endpoint relating to ulcer healing
- *Wound area reduction* is a valid endpoint but must be confirmed by tracing or photograph.
- *Use of 50% reduction in wound surface area* over time is a useful outcome
- *Time to healing* is an important outcome
- *Changes in the wound condition* needs to be supported by a *validated scoring system or supported by an objective measure*, for example a photograph
- *Biological markers* should be clearly predefined and a clinically relevant unit of change should be specified; reliable and valid quantitative assessment methods should be used
- *Wound infection* as a primary outcome marker, should be clearly predefined. Binary measure of presence/absence or a composite score focusing on clinical signs and symptoms should be used
- *Pain reduction:* when using pain as an outcome measure, it is important to predefine the amount of wound pain reduction that is clinically important
- *Surrogate parameters* such as symptoms and signs, or composite endpoints such as scales can be used as primary endpoints, but it is essential that both their basic definition and what is considered to be a clinically relevant difference are predefined. When used as a primary endpoint, it is must be verified by an independent evaluator.
- When assessing dressing performance in an objective manner, with a focus on a specific aspect of symptom management, a comparative study may not be needed; the relevant data could be better assessed using a cohort study with a standardized, reproducible and validated protocol that includes resource utilization
- HRQoL assessments must be based on tools with established psychometrics
- In order to maximise the value of investments in clinical research, studies should be designed to address the relative cost-effectiveness of alternatives from the outset as well as their safety and effectiveness. (Number and sizes of dressings used per wound dressing changes must be properly collected.)

Study design considerations that apply to wound management research:

The design of studies is always debated as different audiences have different requirements, but researchers/clinicians must consider:

- Characteristics of the target study group[1]
- Definition of 'non-healing' wounds if that is the patient group
- Wound types
- Study protocol /methodology
- Setting of care
- Inclusion criteria
- Exclusion criteria
- Dressing and cover dressing types
- Type of study: multicentre vs. single-centre trials
- Study and follow-up period duration: if the primary endpoint is closure, a 12 weeks study period is recommended. However, when selecting an appropriate study duration, the types of ulcer and the relevant outcome(s) must be considered
- A clear description of the control treatment or standard care

Aetiology and basic standard of care in non-healing wounds

- It is essential that standard care procedures/regimens used are consistent to minimise variability and enable assessment of the treatment effect.
  Standard cares can include:
  - Offloading
  - Optimising the general condition of the patient
  - Nutritional support
  - Maintenance of a moist wound environment
  - Removal of infected or necrotic tissues
  - Wound cleansing
  - Compression therapy for venous stasis ulcers
  - Establishing adequate blood circulation or perfusion
  - Bowel and bladder care for patients with pressure ulcers at risk of contamination

[1] N.B. sometimes there is conflict between the data requirements of authorities making decisions on reimbursement, and those of clinicians who need to know if a treatment works in routine practice. From the clinician's perspective, it is desirable to recruit a broad range of patients to studies with the minimum possible exclusion criteria