

Outcomes in controlled and comparative studies on non-healing wounds: Recommendations to improve the quality of evidence in wound management

Summary¹

Editorial board

F. Gottrup¹ MD, DMSci, Professor of Surgery, Chair of the EWMA Patient Outcome Group;

J. Apelqvist^{2,3} MD, PhD, Senior Consultant, Associate Professor, Executive member of the EWMA Patient Outcome Group;

P. Price⁴ PhD, CHPsychol, Dean and Head of School of Healthcare Studies, Executive member of the EWMA Patient Outcome Group;

¹ Bispebjerg University Hospital, Copenhagen, Denmark;

² Malmö University Hospital, Sweden;

³ University of Lund, Sweden;

⁴ Cardiff University, UK.

Evidence based clinical practice is difficult to achieve due to confusion about the value of the various approaches to wound management. To address this, the European Wound Management Association (EWMA) set up a Patient Outcome Group whose remit was to produce recommendations on clinical data collection in wound care. The document, produced by the group and published by JWC¹, identifies criteria for producing precise outcomes in both randomised controlled trials and clinical studies, and describes how to ensure studies are consistent and reproducible. This summary gives a short presentation of the content of the full document.

Background

Non-healing wounds are a significant problem for health-care systems worldwide. In the industrialised world, almost 1–1.5% of the population will have a problem wound at any one time. Furthermore, wound management is expensive: e-g. in Europe the average cost per episode is €6,650 for leg ulcers and €10,000 for foot ulcers, which accounts for 2–4% of health-care budgets.

For these reasons there is an urgent need to review wound strategies and treatments in order to reduce the burden of care in an efficient and cost-effective way.

A primary question is which interventions, technologies and dressing materials are the best from those available? Ongoing controversy surrounds the value of various approaches to wound management and care. There is a need to consider alternative ways of achieving the highest level of evidence required for this patient group.

Quality of evidence in wound management is especially interesting from the following perspectives:

- From the *clinical perspective* the question is which interventions, technologies and dressing materials are the best from the point of view of a single patient or group of patients, where the primary focus is healing and the absence of complications.
Wound management has a paucity of high-quality evidence, as studies are often based on inadequate sample sizes, have short follow-up periods, non-random allocation to treatment groups, non-blinded assessment of outcomes, and poorly described control groups and concurrent interventions.
- From the *policy maker and health-care system perspectives* two issues arise:

¹ The document was published in Journal of Wound Care, Vol. 19, Iss. 6, 6 June 2010, pp 237-268

- Whether or not a particular product or intervention is safe and effective when used as indicated — this is a question of regulatory approval.
- Whether or not the product or intervention represents a cost-effective use of funds.

Too few good quality clinical or economic studies in wound care have resulted in challenges to the reimbursement of modern dressings in favour of supposedly better value traditional products.

- From the *industry perspective* (medical device industry) the challenge is that the standard of care and evidence requirements for reimbursement may be different in each country and that large investments in evidence are rarely justified by the pace of innovation and size of markets for most wound care products.

The **aim** of the document is to provide recommendations on how to achieve rigorous endpoints/outcomes in studies on wound management and to describe an approach that will enable the design of RCTs and clinical studies to be both consistent and reproducible in order to reach a higher quality of evidence in wound management.

Definition of endpoints/outcomes

Study *endpoints* or *outcomes* are the key stone in the evidence discussion. To clarify the basic premises of the discussion, the terminology needs to be clarified.

An endpoint/outcome parameter 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.

In the past, the most commonly used *clinical* outcome (endpoint that directly relates to outcome) was visible reduction in wound size, particularly intact skin (full healing).

The development of tests and techniques to improve tissue sampling and analysis, imaging technology and scientific progress in cellular and molecular biology has enabled the development of more 'objective' wound outcome parameters (surrogate outcome parameters) that relate to both the wound condition and the treatment intervention being assessed (for example, exudation rate, pain, granulation rate, resolution of necrosis or infection).

A surrogate endpoint/outcome parameter is defined as a physical sign or a laboratory measurement that can be used as a substitute for a clinically meaningful endpoint, effectively directly measuring how a patient feels, functions or survives.

The challenge, in non-healing wounds, is that these types of endpoints/outcome parameters are difficult to achieve and maintain. If the only gold standard was total wound closure, no therapy would ever be considered efficacious. Alternative endpoints are therefore needed.

Material and methods

Material: The background information, evaluations and recommendations of the document are based on a collection of a large amount of available guidance for evidence collection and an analysis of recent RCTs and comparative studies. To achieve an updated status (2003–2009) on how endpoints/outcome parameters are used, defined and evaluated, we performed a literature search on chronic/problem wounds/ulcers, with the

objective of examining and registering their use of endpoints, the quality of their endpoint definitions and the robustness of their methodologies.

Discussions with various stakeholders within and outside the framework of the EWMA Patient Outcome Group have also provided a basis for the structure and content of the document.

Methods: To establish a basis for the recommendations and statements related to study designs and use of outcome measures in wound management, data collection issues, concepts and terms were discussed and used in the document.

The challenge has been to control the heterogeneity of individual patients, concurrent disease states and confounding factors, as well as variations in the type, site and condition of wounds and differences in health-care organisations. These problems cannot be solved by enrolling more subjects into a study.

Currently, the majority of wound management studies recruit patients with one wound aetiology. However, the development of more targeted strategies specific to different phases of treatment (e.g. debridement) means that the condition of the wound (e.g. exudate rate, pain and necrosis) may be a better inclusion criterion.

Furthermore the following perspectives and terms have been taken into consideration:

From the clinical research perspective there is a need to be aware of the strengths and limitations of different study designs if they are to effectively evaluate which health-care practices are worth considering for different patients in different health contexts. Key issues are, for example, use of a study protocol, problems related to heterogeneity of the study population and underlying conditions.

From an industry perspective, external evidence needs are set by the requirements of national regulatory and reimbursement authorities, and other payers. When developing a new product, there are also internal needs for evidence, which mirror the phases of the development process. When focusing on payment or reimbursement for a new product, the key issue will often be budgetary impact and/or cost-effectiveness, rather than healing.

The document also discusses the importance of a generally accepted definition of 'standard care' in connection with data collection in wound management. 'Standard care' refers to generally accepted wound care procedures and the management of underlying disease, outside of the investigational product/device or drug that will be used in the clinical trial/evaluation. It is essential that the standard care procedures/regimens used are consistent as this will minimise variability and enable assessment of the treatment effect.

Results

Following an evaluation of abstracts from the recent RCTs and comparative studies by three reviewers, 176 articles found in the literature search were selected for analysis. Many studies measured multiple endpoints/outcome parameters — in total, this analysis generated a list of 313 different endpoints.

The endpoints were divided into the following categories (the percentages represent each category's proportion of the 313 registered endpoints):

- Reduction rate (24.1%)
- Wound closure (16.9%)
- Healing time (9%)
- Change in wound condition (9%)
- Biomarkers and bacteriology (4.5%)

- Circulation (1.9%)
- Infection signs (4.5%)
- Symptoms and signs (13.2%)
- Dressing performance (7.0%)
- Quality of life (5.8%)
- Costs and resources used (4.5%).

The findings of the analysis were used as a basis for discussing and suggesting procedures for the successful measurement of each of the types of endpoint categories defined.

In general, it was found that a substantial number of endpoints (45%) were either not predefined or insufficiently defined. As part of the analysis, the degree of robustness of the measurement techniques used in studies² and the degree of reproducibility³ were evaluated. In 70% of cases, a standardised or clearly defined measurement technique was used to examine the endpoint (e.g. computerised planimetry or a standardised evaluation method). These were defined as meeting the criteria for an acceptable degree of robustness. However, 76% of these did not meet the criteria for reproducibility.

The analysis and discussion resulted in a number of recommendations ('statements') on use of endpoints in RCTs and comparative studies on non-healing wounds (See table 1).

Discussion

When evaluating interventions in wound management it is a challenge to avoid performance bias. Designing studies with the aim of obtaining sufficient information regarding outcomes is particularly hazardous. The document therefore discusses and provides recommendations regarding some of the considerations that should be made when designing studies on interventions for the treatment of wounds.

The definition of non-healing wounds is still discussed. We suggest that the definition 'chronic' be replaced with the definition 'non-healing' as this better reflects the clinical problems experienced by such patients. It is also suggested that multicentre trials should imply great efforts to enrol sufficient numbers at each site and a high degree of protocol standardisation. Another issue brought forward is the selection of an appropriate study period. Recommendations from various institutions vary from 2 weeks to 12 months. We recommend that the type(s) of ulcer and relevant natural outcome is considered when selecting the study duration.

Some common methodological errors in wound-dressing studies and a Checklist for objectives and endpoints/outcomes in clinical trials are described in table 2 and 3, included in this summary⁴.

Conclusion

The document provides recommendations to improve the quality of evidence in wound management. This is achieved by formulating a set of statements within the following areas:

- Different types of evidence required by different authorities
- Evaluation of outcome
- Outcome: endpoints in RCTs and comparative studies on non-healing wounds
- Performance bias and interpretation of findings

² Defined as a level of information about the measurement technique, such that others could replicate the data collection in an identical way.

³ Defined as the inclusion of a verifiable source of data, e.g. photos, to secure the possibility of validation from an external source by reproducing the study, or the involvement of an external validation source as part of the study design.

⁴ Table 15 and 16 in the full document.

Table 1: Statements on endpoints/outcome parameters

- Wound closure, defined as total epithelialisation without discharge, is the most important endpoint relating to ulcer healing. It must be confirmed by an independent source (photography) and there must be sufficient follow-up to confirm healing
- Wound area reduction is a valid endpoint with regard to wound healing but it must be confirmed by tracing and include a predefined relevant cut-off to ensure that 'reduction rate error' (described in section: 'reduction rate') does not occur
- There is enough evidence to support the use of a 50% reduction in wound surface area over time as a useful outcome, provided that the initial wound size and the measurement technique are taken into consideration. The time interval used in such assessment will vary depending on the wound type. Any reduction of less than 50% cannot be supported by the current literature; in these instances, more objective measures of size reduction must be used
- Time to heal is an important outcome. However, the study protocol must consider the substantial methodological difficulties entailed, particularly confirmation of the exact date of healing for each patient during the specified observation period. To date, the accepted time interval for resource studies is one year
- There is an urgent need for a validated scoring system with regard to wound condition
- When using changes in the wound condition as an outcome parameter, they must be predefined and measured in such a way that they can be validated independently, wherever possible (for instance, by photograph)
- When using biological markers as a primary outcome, they should be clearly predefined, and a clinically relevant unit of change should be specified; reliable and valid quantitative assessment methods should be used
- When using wound infection as a primary outcome marker, it should be clearly predefined. At present, this could be either a binary measure of presence/absence or a composite score focusing on clinical signs and symptoms
- Regardless of the assessment tool used, when using pain as an outcome measure it is important to pre-define the amount of wound pain reduction that is clinically important
- When surrogate parameters such as symptoms and signs, or composite endpoints such as scales, are used as primary endpoints, 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 favourable for it to 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 standardised, reproducible and validated protocol that includes resource utilisation (when appropriate)
- HRQoL assessments must be based on tools with established psychometrics
- The type of assessment must fit with the purpose of the data collection: if HRQoL data are to be used for health technology assessment reviews, then generic and/or utility methods must be included
- When cost is used as an outcome parameter in wound management, it is essential to measure all the quantities of resources used and then add the value of those resources, according to a predefined protocol. It is recommended that resource use and cost are shown separately
- Wherever resources have alternative uses, decisions on the adoption of new technologies or new procedures cannot be made on the basis of clinical outcomes alone. Rational choice requires evidence of the costs and benefits of alternatives
- 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.

A full list of statements is found in the article published in *Journal of Wound Care*, Vol. 19, Iss. 6, 6 June 2010, pp 237-268).

By formulating these recommendations (statements) we aim to provide guidance with regards to choosing

and defining endpoints/ outcome measures (primary and secondary) when preparing an RCT or comparative study.

The key messages of the document can be summarized in the following messages:

1. A substantial number of publications exist – but we need to increase quality of evidence.
2. Consistency in measuring endpoints/outcomes improves quality. To reach consistency it is important to:
 - Use pre-defined and robust outcomes
 - Adapt outcomes to the intervention under investigation
 - Use the best evidence available
3. Using intact skin/healing as an outcome measure is not always possible/suitable – using the patient focus clarifies which other endpoints are relevant.
4. The term ‘chronic’ wound should be replaced with ‘non-healing’ wound.
5. ”Basic care” must be standardised.
6. The Patient Outcome Group does not reject RCTs in wound management, but advocates that clinical trials using alternative endpoints to healing are evaluated as being equally suitable for the evaluation of various wound interventions.

Table 2: 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
- Randomisation 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

Table 3: Checklist for objectives and outcomes in clinical trials

- Are the intervention and control (e.g., usual care) described in detail?
- Has the target patient population been specified?
- Has the degree of benefit from the intervention on a particular outcome, and the time frame, been specified?
- Has the primary outcome, including how and when it is to be measured, been specified?
- Have any secondary outcomes been pre-specified in similar detail? Outcomes
- Are the outcomes clinically relevant, objective (wherever feasible) and unambiguous?
- Can the outcomes be measured for all patients and, where possible, assessed with researchers blinded to the allocated treatment?
- Is the study explicit in the frequency and duration of outcome measurement?
- Has the study been specially planned from a statistical viewpoint when multiple outcomes are measured?
- If the outcome is a surrogate, will it adequately reflect a main outcome, and is there an indication of how much a benefit observed on the surrogate outcome will translate to a benefit on a main outcome?

(Reference: Appendix B, Quality of Literature, ECRI Institute Study Quality Assessment Instrument, Negative Pressure Wound Therapy Devices, www.ecri.org)

Key references

- Bell-Syer S, Brady M, Bruce J, Cullum N, Foxlee R, Jull A, Margolis D, McInnes L, Nelson A, O'Meara S, Ubbink D. Letter: Evidence-based wound care in the UK: A response to David Leapers Editorial in International Wound Journal April 2009 6 (2). 2009 Int Wound J; 6:306-9.
- Biancari F, Salenius JP, Heikkinen M, Luther M, Ylönen K, Lepäntalo M. Risk-scoring method for prediction of 30-day postoperative outcome after infrainguinal surgical revascularization for critical lower-limb ischemia: a Finnvasc registry study. World J Surg 2007;31:217-225.
- Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clinical Pharmacol Ther 2001;69:89-95
- Bouza C, Munoz A, Amata JM. Efficacy of modern dressings in the treatment of leg ulcers: a systematic review. Wound Rep Reg 2005; 13: 218-229.
- Briggs M, Closs SJ (2006) Patients' perceptions of the impact of treatments and products on their pain experience of leg ulcer pain. J Wound Care 15 (8): 333-337
- Chaby G, Senet P, Veneau M et al. Dressings for acute and chronic wounds. A systematic review. Arch Dermatol 2007; 143: 1297-1304.
- Carter MJ. Evidence-based medicine: An overview of key concepts. Ostomy Wound Manage 2010; 56: 68-85.
- De Gruttola, et al Considerations in the Evaluation of Surrogate Endpoints in Clinical Trials: Summary of a National Institutes of Health Workshop Control Clin Trials 2001; 22:485-502
- Drummond MF, Schulpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes*. Oxford University Press, Third Edition, 2005
- Enoch S, Price PE. Cellular, molecular and biochemical differences in the pathophysiology of healing between acute wounds, chronic wounds, and wounds in the aged. World Wide Wounds August 2004; Available from www.worldwidewounds.com/2004/august/Enoch/Pathophysiology-Of-Healing.html
- Falanga V, Saap LJ, Ozonoff A. Wound bed score and its correlation with healing of chronic wounds. Dermatol Ther 2006;19:383-90
- Gershtar M, Apelqvist J, Eneroth M, Larsson J, Nyberg P, Thörne J Complexity of factors related to outcome of neuropathic and neuroischemic/ischemic diabetic foot ulcers; a cohort study Diabetologia. 2009 Mar;52(3):398-407
- Gottrup F: Evidence is a challenge in wound management. Editorial. Lower Extremity Wounds. 2006; 5: 74-65.

- Gottrup, F. & Apelqvist, J.: The challenge of using randomized trials in wound healing, *Br J Surg* 2010; 97: 303–304
- Gottup F, Appelqvist 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: 237-268
- Grey J E, Leaper D, Harding K: How to measure success in treating chronic leg ulcers (Editorial), *BMJ* 2009;338:b1434
- Hinchliffe RJ, Vaik GD, Apelqvist J, Armstrong DG, Bakker K, Game FL et al. A systematic review of the effectiveness of interventions to enhance the healing of chronic ulcers of the foot in diabetes. *Diabetes Metab Res Rev* 2008; 24(Suppl 1): S119–S144.
- Horkan L, Stansfield G, Miller M: An analysis of systematic reviews undertaken on standard advanced wound dressings in the last 10 years, *Journal of Wound Care*, Vol 18 No 7, July 2009
- Leaper D. Evidence based wound care in the UK (Editorial). *Int Wound J* 2009; 6: 89-91
- Levine, Susan; Petra Nass & Theresa Røgstad; Effectiveness Guidance Document: Methodological Guidance for the Design of Comparative Effectiveness Studies, Devices for Local Treatment of Chronic Wounds , CMTP Center for Medical Technology Policy, Version 1.0 Published August 2009
- Lipsky B A, Polis A B, Lantz K C, Norquist J M, Abramson M A: The value of a wound score for diabetic foot infections in predicting treatment outcome: A prospective analysis from the SIDESTEP trial, *Wound Rep Reg*, Volume 17, Issue 5, 2009, 671-677
- Little C, McDonald J, Jenkins M G, McCarron P: *An overview of techniques used to measure wound area and volume*, *J Wound Care* 2009; 18: 250-253
- Matousek S., A.K. Deva, Mani R: Outcome Measurements in Wound Healing Are Not Inclusive: A Way Forward Lower Extremity Wounds 2007; 6: 284–290
- Moore K, McCallion R, Searle RJ, Stacey MC, Harding KG. Prediction and monitoring the therapeutic response of chronic dermal wounds. *Int Wound J* 2006; 3:89-96.
- Neumann PJ, Tunis SR. Medicare and medical technology – The growing demand for relevant outcomes. *N Engl J med* 2010; 362: 377-379.
- Palfreyman S, Nelson EA, Michaels JA. Dressings for venous leg ulcers: systematic review and meta-analysis. *BMJ* 2007; 335: 244.
- Peinemann F, McGauran N, Sauerland S, Lange S. Negative pressure wound therapy: potential publication bias caused by lack of access to unpublished study results data. *BMC Med Res Methodol* 2008;8:4
- Penhallow K. A review of studies that examine the impact of infection on the normal wound-healing process. *J Wound Care* 2005;14:123-6
- Persoon A, Heinen MM, van der Vleuten CJ, de Rooij MJ, van de Kerkhof PC, van Achterberg T. Leg ulcers: a review of their impact on daily life. *J Clin Nurs* 2004; 13(3): 341-54.
- Posnett J, Gottrup F, Lundgren H, Saal G, , The resource impact of wounds on health-care providers in Europe, *J of Wound Care* 2009; 18: 154-161
- Price P E, Fagervik-Morton, H, Mudge, EJ, Hilde Beele, Jose Contreras Ruiz, Theis Huldts Nystrom, Christina Lindholm, Sylvie Maume, Britta Melby-Østergaard, Yolanda Peter, Marco Romanelli, Salla Seppänen, Thomas E Serena, Gary Sibbald, Jose Verdú Soriano, Wendy White, Uwe Wollina, Kevin Y Woo, Carolyn Wyndham-White, K G Harding. Dressing related pain in patients with chronic wounds: an international perspective. *Int Wound Journal* 2008; 5: 159-171
- Price P. The challenge of outcome measures in chronic wounds. *J Wound Care*. 1999;8:306-8
- Prompers L, Huijbert M, Apelqvist J et al. Prediction of outcome in individuals with diabetes and foot ulcers: focus on the difference between individuals with and without peripheral artery disease. The EURODIALE-study. *Diabetologia* 2008 51 (5) 747-55
- Prompers L, Huijberts M, Schaper N, Apelqvist J, Bakker K, Edmonds M, Holstein P, Jude E, Jirkovska A, Mauricio D, Piaggese A, Reike H, Spraul M, Van Ácker K, Van Baal S, Van Merode F, Uccioli L, Urbancic V and G Ragnarson Tennvall. Resource utilisation and costs associated with the treatment of diabetic foot *Diabetologia* 2008; 51: 1826-1834
- Ragnarsson-Tennvall G, Apelqvist J, Cost-effective management of diabetic foot ulcers. *PharmacoEconomics*. 1997;12:42-53 .
- Ryan S, Eager C, Sibbald RG. Venous leg ulcer pain. *Ostomy Wound Manage* 2003; 49(4 Suppl): 16-23
- Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS. Evidence-based medicine: what is and what isn't. *BMJ* 1996: 312: 71-72.
- Vaneau M, Chaby G, Guillot B, Martel P, Senet P, Teot L, Chosidow O. Consensus panel recommendations for chronic and acute wound dressing. *Arch Dermatol* 2007; 143: 1291-1294.
- Wolcott RD, Rhoads DD, Bennett ME, Wolcott BM, Gogokhia L, Costerton JW, Dowd SE. Chronic wounds and the medical biofilm paradigm. *JWC* 2010 19 45-53

Useful documents giving guidance for evidence collection are listed in table 4.

Acknowledgements:

The authors thank the following for their invaluable contribution to finalizing this document:

- Martin Abel, Dr rer nat, Head of Medical & Regulatory Affairs, Lohmann & Rauscher GmbH & Co KG; Germany
- John Posnett, BA, DPhil, Vice President of Health Economics, Smith & Nephew, UK

Coordination: Julie Bjerregaard, EWMA Secretariat

Table 4: Useful documents giving guidance for evidence collection

- AQUA Institute, www.aqua-institut.de
- DIN ISO EN 14155-1: 'Clinical investigation of medical devices for human subjects – Part 1: General requirements'. Part 2: Clinical investigation plans' (edited by Beuth Verlag, <http://www.beuth.de>)
- FDA: Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment Food and Drug Administration, June 2006 www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071324.pdf
- FDA Wound Healing Clinical Focus Group. Guidance for industry: chronic cutaneous ulcer and burn wounds — developing products for treatment. Wound Rep Reg 2001; 9: 258-268 ICH (International Conference of Harmonisation) e.g. Topic E 6: Guideline for Good Clinical Practice in the European Community, www.ich.org
- IQWiG / D: General methods, www.iqwig.de/general-methods.428.en.html
- IQWiG / D: Cost-benefit assessment ISPOR guidance www.ispor.org/PEguidelines/index.asp
- MEDDEV 2, 12-2 May 2004: Medical Devices: Guidance Document – Guidelines on post market clinical follow-up, http://ec.europa.eu/enterprise/sectors/medical-devices/files/meddev/2_12-2_05-2004_en.pdf
- MEDDEV 2.7.1. Dec 2009: Guideline on Medical Devices – Clinical evaluation: Guide for manufacturers and notified bodies, http://ec.europa.eu/enterprise/sectors/medical-devices/files/meddev/2_7_1rev_3_en.pdf
- Nice/UK: Guideline manual 2009 www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/GuidelinesManual2009.jsp www.iqwig.de/cost-benefit-assessment.736.en.html
- SIGN 50: A guideline developer's handbook (SIGN: Scottish Intercollegiate Guidelines Network) January 2008, especially the Annex B 'Key of evidence and grades of recommendations' and Annex C 'Methodology Checklist' www.sign.ac.uk/guidelines/fulltext/50/index.html
- The Consort Statement: Revised recommendations for improving the quality of reports of parallel-group randomised trials, www.consort-statement.org/ Mohr, D., Schultz, K.F., Altman, D.G. (for the Consort Group). Lancet 2001; 357: 1191-1194
- The Cochrane Collaboration, www.cochrane.org