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## **Reflections on the Recommendations of the European Wound Management Association Patient Outcomes Group**

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The European Wound Management Association (EWMA) Patient Outcomes Group recently delivered 29 diverse recommendations about the conduct and reporting of wound care research and we have been invited to respond.[1] At almost thirty pages long, this is a substantial piece of work and rather than address every detail we would like to focus on the process by which the recommendations were derived and the consequences of that process.

First to say that we applaud the aims of the document; clearly there is a problem with the validity and relevance of wounds research evidence for decision makers.[2] Perhaps if the Patient Outcomes Group had followed well established processes for the production of clinical practice guidelines, the recommendations are more likely to have been valid, embraced by the relevant community and implemented.

Research recommendations are not the same as guidelines for clinical practice but we see no difference in the principles of clinical guideline development and the development of guidelines for researchers about research conduct. The same pitfalls exist for both if due process is not observed. If guideline panels are not representative of the breadth and depth of expertise in the relevant field, if rigorous methodology is not followed in

gathering and synthesising the evidence on which recommendations are based, if there is not clear independence of the guideline developers from those who may benefit and no clear conflict of interest policy and if such documents are not extensively peer reviewed before publication then guidelines are substantially weakened in authority and validity. If we compare the EWMA document with the process outlined in the internationally adopted AGREE instrument (for clinical practice guidelines) we quickly see how far these fall short and the consequences.[3]

AGREE emphasises six domains in which guideline developers should strive to minimise bias in their processes and instead promote rigour and relevance. These domains are:

1. **Scope and purpose.** The focus and purpose of recommendations should be unambiguous and clear.
2. **Stakeholder involvement.** All relevant professional and patient groups should be represented.
3. **Rigour of development.** Recommendations should be based on comprehensive summaries of research; the process by which evidence was selected should be clearly described; the methods used for formulating recommendations and decision making should be transparent; there should be explicit links between recommendations and the supporting evidence; a document should be peer reviewed before publication.
4. **Clarity and Presentation.** Recommendations should be specific and unambiguous.
5. **Applicability.** Possible barriers to implementation, including cost, should be considered.
6. **Editorial independence.** Guidelines should be editorially independent of any funding; there should be an explicit statement that the views and interests of funders have not influenced the recommendations. Conflicts of interest should be clearly recorded.

Whilst the EWMA document meets some of the criteria outlined it falls short in several important domains, particularly editorial independence, stakeholder involvement and rigour of development.

### **Editorial independence and stakeholder involvement**

The main stakeholders were eight individuals, at least one of whom is employed by a pharmaceutical company, plus unnamed representatives from nine pharmaceutical companies. Clearly the pharmaceutical industry has played a key role in this document but the precise nature of this role is opaque in terms of scientific, editorial and financial support. These issues are not irrelevant because as the document states, randomised controlled trials (RCTs) are expensive and the authors state “Very few wound care products *have a sufficiently large potential market to justify this investment*”. Given the relative imbalances in the EWMA Patient Outcome Group membership between representatives of industry, of independent methodologists and of patients, there are likely to be concerns as to the intended beneficiaries of the recommendations.

The fact that the group chose not to seek the input of medical statisticians and epidemiologists is completely inexplicable (since this territory is fundamentally statistical and epidemiological). Had they done this, the recommendations are likely to have presented a more sophisticated consideration of the statistical implications of choosing alternative outcomes. For example, time to healing as an outcome offers the opportunity of dealing with censoring (a huge issue in wounds trials where randomised patients frequently do not appear in the analysis). [4] The group reports that there are substantial difficulties with using time to healing as an endpoint. The only methodological difficulty actually mentioned is the confirmation of the exact date of healing for each patient. It is true that when wounds are concealed by bandages determination of exact date of healing can be difficult and that there may be a subjective element in the decision that healing is complete. In a randomised trial, these difficulties are present in all participant groups and so should not cause any bias, and digital photography makes blinded assessment of healing possible. We have

not encountered any difficulties during the conduct of several large RCTs of wound treatments, nor have others. [5–8]

The group’s consideration of endpoints would also have benefited from methodological input. They state that there is “...enough evidence to support the use of a 50% reduction in wound surface areas as a useful outcome” but as they do not clearly cite this evidence readers cannot determine what the evidence is and whether it is from clinical prognostic studies or treatment evaluations, nor the type of wounds for which this evidence applies (important since wounds of different aetiologies have different healing trajectories). Is a reduction in wound area really a valid endpoint for pressure ulcers? Is there really research which demonstrates that surrogate outcomes such as “change in area” are valid and reliable in the context of research aiming to measure relative treatment effects?

Observational study designs, as the Group indicates, have huge potential to complement RCTs and we are currently piloting a register of complex wounds. We have already learnt that the collection of prospective, observational data (such as in a register) is as, or more, challenging than conducting RCTs.[9] We are far from a world where observational data can eradicate the need for experimental designs because the problem of confounding (particularly by unknown confounders) is difficult to eradicate. The US Center for Medical Technology Policy produced methodological guidance for the design of comparative effectiveness studies in chronic wounds in 2009[10] and recommended RCTs, saying also that non-randomised studies may be considered if they are based on a priori hypotheses and that “*advanced methods to adjust for possible baseline differences [confounders] including instrumental variable analysis and propensity scoring should be used*”. It is important for the wounds research community to recognise that non-randomised designs have serious limitations with regards to estimating treatment effectiveness (due to the likelihood of confounding) and very sophisticated methodologies are required to reduce the possibility of drawing the wrong conclusions. [11, 12] For example, the

analysis of observational data produced misleading treatment effects for HIV drugs, when compared with trial results.[13]

But it is the privileging of the views of the pharmaceutical industry over those of patients, by a group which purports to be about patients, which is most concerning. As the AGREE instrument reminds us, patients must be at the table when “experts” produce guidelines for clinical practice.[3] So it is also the case that they must be represented in a conversation about clinical research and patient outcomes. We must listen to patients and carers in order to find out which research questions and outcomes matter to them. We are currently, in collaboration with the James Lind Alliance, [14] establishing the James Lind Alliance Pressure Ulcer Partnership. Given the lack of patient involvement in research agenda setting and the narrow evidence-base informing clinical decision making, the aim is to establish a partnership of patients, carers and clinicians to identify research priorities in the prevention and management of pressure ulcers, before moving on to replicate the process in other wound areas.[15]

### **Rigour of development**

Groups who develop recommendations with the aim of altering people’s professional behaviour have a responsibility to ensure that their processes and outputs are as transparent and rigorous as they can be. Unfortunately it is difficult to judge the rigour of these recommendations as the methods are not explicit so we cannot tell if they are based on systematic reviews of relevant (methodological) research, the methods by which the recommendations were formulated are not stated and they are not explicitly linked with the supporting evidence.[3]

### **Conclusions**

In a clinical area where RCTs have been unfairly criticised,[16,17] it is refreshing that this report acknowledges the importance and feasibility of conducting robust wound care trials. However rather than adopting ‘a framework similar to the CONSORT agreement *for conducting clinical studies*’ as recommended, we should be adopting CONSORT itself, which was

designed to be applied across health care. [18] We need to work to dispel the myth that wound care RCTs are somehow different or more difficult to undertake than in other areas. Not only is there an ever increasing body of large, high-quality trials of wound care treatments, but RCTs are routinely conducted in other challenging disease areas (e.g. cancer, heart failure and diabetes) where patients are also elderly and have multiple co-morbidities. You could argue that research in wounds is easier in many ways; the wound is visible and measureable, and (unlike cancer), you can see when it's gone.

The EWMA document takes us part of the way along the road to improving the quality of wounds research but it fails for the same reason that wounds research is generally of poor quality; the Group did not see the importance of having cutting edge methodologists as well as patients in their team. Without the input of epidemiologists and medical statisticians then trials are of poor quality and observational research will be positively dangerous. Without the involvement of patients we run the risk of doing research about the wrong things and measuring outcomes that don't matter.

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