

Research Waste in Atopic Eczema Trials—Just the Tip of the Iceberg

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Clinical trials often continue to be undertaken even though the effectiveness of the intervention under consideration has already been demonstrated. In addition, vehicle- or placebo-controlled studies predominate over head-to-head comparisons, although the latter would be more informative for clinicians in guiding patient management. This creates research waste, and both investigators and funders are to blame. Wilkes et al. used a network analysis approach to show duplication of effort in trials assessing topical calcineurin inhibitors and corticosteroids as treatment options for atopic eczema. Unfortunately, this is just the tip of the research waste iceberg.

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In 2009, a landmark article published in the *Lancet* (Chalmers and Glasziou, 2009) lamented avoidable waste in the production and reporting of research evidence, and one important aspect of this wastage was the conduct of studies that were unnecessary, because the questions they proposed were answered satisfactorily with existing evidence. Apparently, many trial investigators are not even aware of the relevant systematic reviews at the time they design their studies (Cooper et al., 2005). Having said that, only around 2,500 systematic reviews are published on an annual basis, and it has been estimated that at least 10,000 systematic reviews are needed to cover the issues addressed in more than half a million annual reports of controlled trials (Patsopoulos et al., 2005). But even if many more systematic reviews are required, essentially redundant clinical trials continue to be conducted. Here is a classic example: A cumulative meta-analysis showed a significant positive effect of tranexamic acid on postoperative bleeding, and a resulting reduction in the need for blood

transfusions. This had been established by 1996, after results from four trials were published (Figure 1) (Ker et al., 2012). Nevertheless, researchers continued to conduct similar studies for years to come. During the same time period, important other questions, for instance the effect of preoperative administration of tranexamic acid on postoperative myocardial infarction and death, remained unresolved, because the studies that had been conducted were too small to provide definitive answers (Figure 1) (Chalmers et al., 2014).

Wilkes et al. (2016) use a network analysis approach, novel to dermatology systematic reviews, highlighting the unnecessarily large number of vehicle-controlled studies in atopic eczema trials. The authors identified a total of 174 randomized controlled trials for atopic eczema treatments in which pimecrolimus, tacrolimus (both calcineurin inhibitors), or topical corticosteroids, at varying strengths, were compared with other interventions. More than 60% of the topical calcineurin inhibitor studies and close to

40% of the topical corticosteroid trials were vehicle controlled.

Not only are there an unnecessarily large number of vehicle-controlled randomized controlled trials, by contrast, the studies that really matter and inform medical decision making in day-to-day clinical practice—direct comparisons between topical calcineurin inhibitors and topical corticosteroids—have not been conducted in sufficient numbers either.

Only the tip of the (research waste) iceberg

Inflated publication numbers of vehicle-controlled clinical trials are only the tip of the iceberg (Figure 2). Glasziou and Chalmers (2009) estimated that approximately 85% of research investment, the equivalent of \$200 billion, is wasted. This estimate does not even take inefficiencies in the regulation and management of research into account. One major problem of scientific research is that publication of negative findings is difficult, resulting from medical journals' bias toward statistically significant "positive" results, which affects journals of all impact factors. This means that important "negative" findings often do not find their way into the public domain, or linger away in the "grey" literature or among stacks of conference abstracts.

Bias is also introduced through the conscious suppression of "negative" evidence, which has been noted, especially in the context of pharmaceutical-sponsored research. In response, the WHO's International Clinical Trials Registry Platform was created to improve transparency, and in some countries, such as the USA, publication of the results of research is now required by law. Nevertheless, public access to the full results of all research remains an aspiration, one that is resisted by researchers and sponsors alike (Chalmers and Glasziou, 2009). The "All Trials" campaign has therefore been a welcome initiative to promote complete publication of trial results. The message is clear and simple: "All trials registered; all results published" (www.alltrials.net). Another step in this direction was marked by the

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Clinical Implications

- Network analysis as part of systematic reviews can help to highlight duplication of effort in clinical research.
- Support for a concerted effort in the international scientific community to direct resources into areas of real scientific and clinical need is warranted.

announcement that clinical trial identification numbers can now be linked to digital object identifiers, allowing rapid online access to all related publications for clinical trials (http://www.eurekalert.org/pub_releases/2016-05/c-cpd051716.php). In addition, the European Medicines Agency recently published comprehensive guidance on the publication of clinical study reports,

which may lead to enhanced transparency. On the other hand, concerns remain that pharmaceutical companies can hold information back when it is deemed to be “confidential” (European Medicines Agency, 2016). Bias is also introduced through the inflated publication of vehicle-controlled studies, noted by Wilkes et al. (2016) in the context of atopic eczema trials,

because the pharmaceutical industry uses such “seeding trials” as a covert instrument to promote specific products.

Unfortunately, research does not always address areas of high priority, either. This is not to say that all research should be directly applicable to patients and clinical practice, as undoubtedly important and often serendipitous advances have been made through basic laboratory research. Nevertheless, we need to ask whether it is justified that over half of research investment is dedicated to basic laboratory research (Collins, 2012), whereas emphasis should instead be placed on the translatability of findings, from bench to bedside.

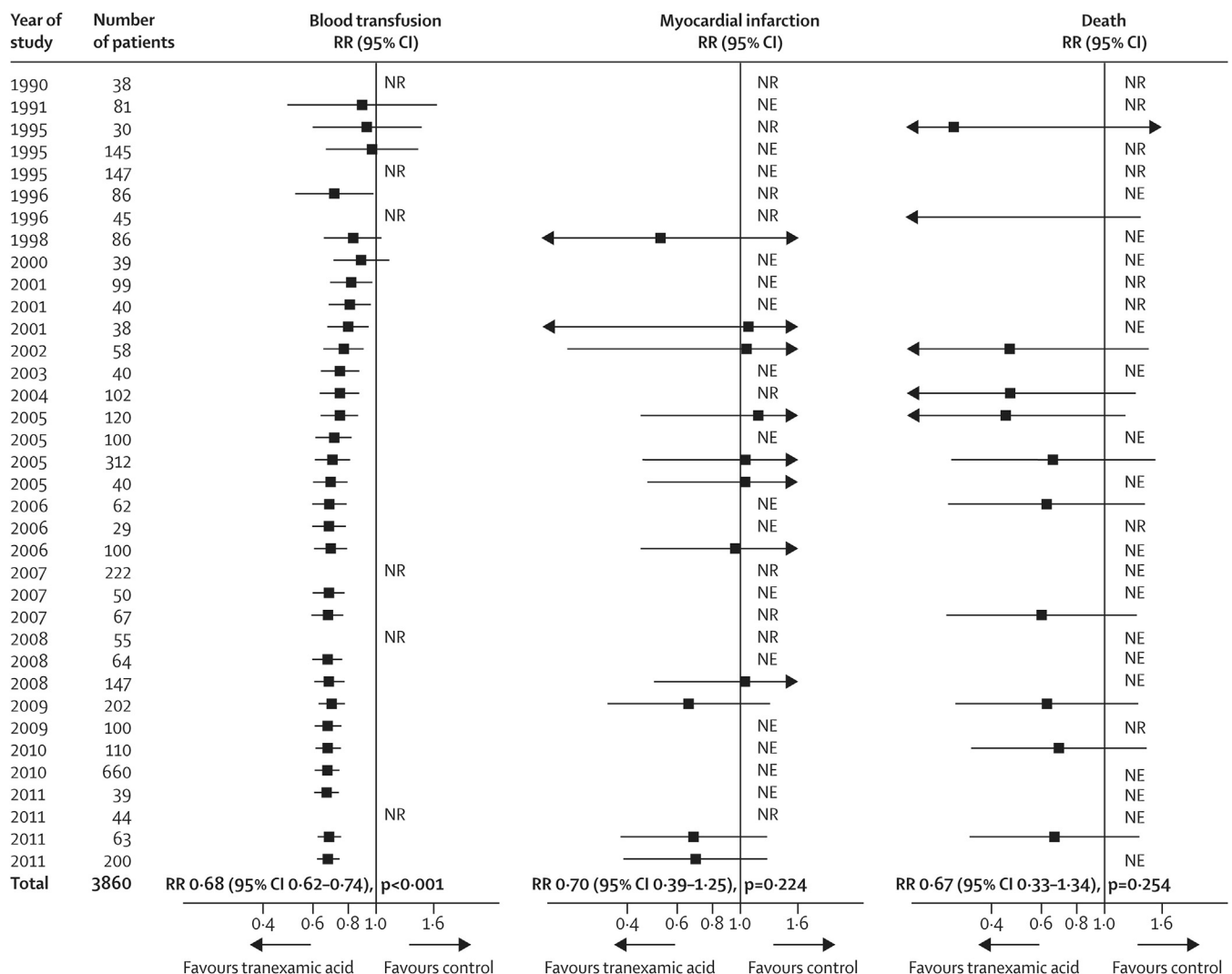


Figure 1. Cumulative meta-analyses of trials using tranexamic acid during surgery. The protective effect of tranexamic acid on the postoperative risk of bleeding and the subsequent need for blood transfusion was already established in 1996. However, scientists continued to conduct trials answering the same question. By contrast, the effect of tranexamic acid on the risk of postoperative myocardial infarction and death remained uncertain even in 2011, as the studies were too small to answer these important questions adequately. CI, confidence interval; NE, no events; NR, not reported; RR, risk ratio. Reprinted from The Lancet, Chalmers et al., 2014, with permission from Elsevier.

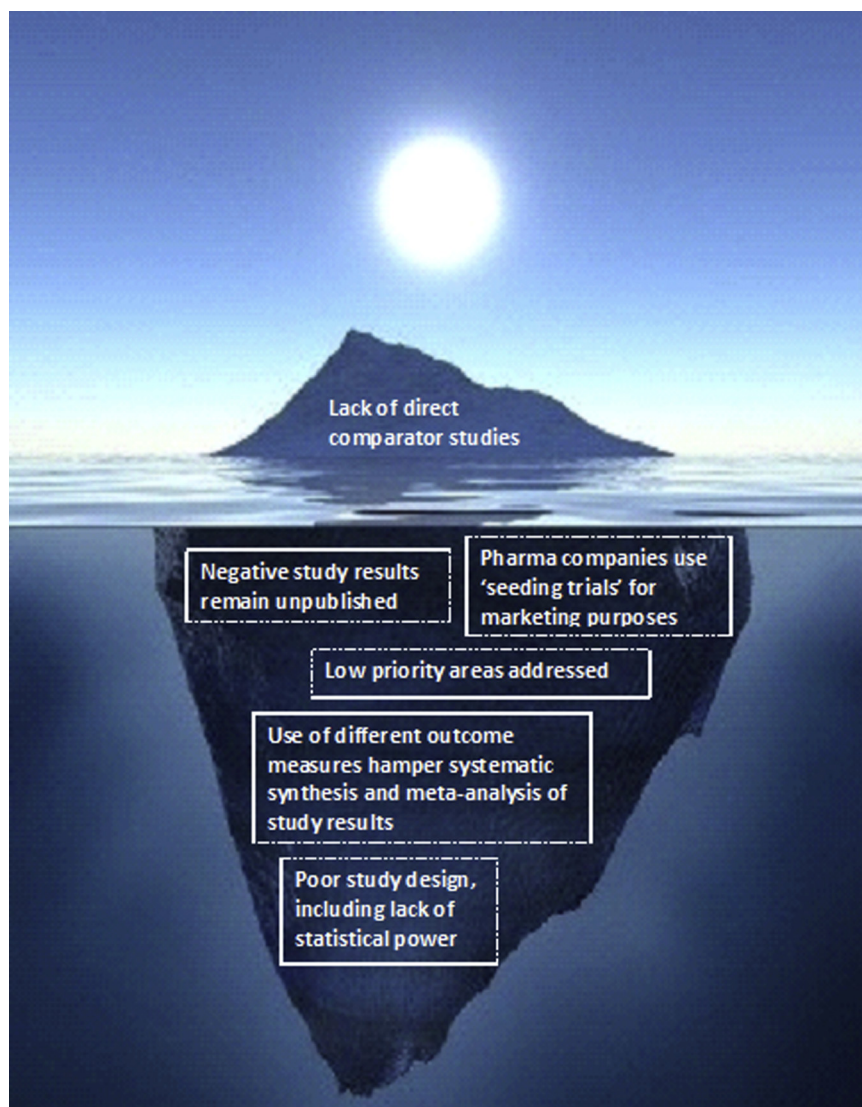


Figure 2. The research waste iceberg. The lack of direct comparator studies highlighted in Wilkes et al.'s (2016) systematic review is only the tip of the iceberg. Other important areas of research waste are poor study design, the fact that negative study results often remain unpublished, the use of diverse study outcomes which hampers systematic synthesis of study evidence as well as the use of "seeding trials" for marketing purposes. Image created by C. Flohr.

Another area that continues to cause headaches to those who conduct systematic reviews is the use of divergent outcomes and outcome measures in clinical trials, hampering direct comparability between studies and meta-analysis of study results. Finally, the main hurdle in reducing waste is poor research itself, commonly caused by inadequacy in study design, such as failure to define clinically meaningful outcomes and outcome measures, lack of statistical power to show whether one treatment is better than another or whether both treatments are equally effective, and, finally, a clinically meaningful interpretation of results. Even if studies are well conducted, they are often not well

reported. For instance, in a survey of highly cited animal studies from seven leading journals (*Science*, *Nature*, *Cell*, *Nature Medicine*, *Nature Genetics*, *Nature Immunology*, and *Nature Biotechnology*), less than 20% of the studies described the randomization processes or whether there had been blinding (Moher et al., 2015).

What can the dermatology community do to reduce research waste?

We therefore ask what the dermatology community can do to reduce research waste. As a good starting point, reporting of study results needs to be improved, and widely adopted guidance, such as Consolidated Standards

of Reporting Trials, has certainly helped to raise standards for randomized controlled trial reporting; it is now required by most dermatology journals, including the *The Journal of Investigative Dermatology*. Similar guidance exists for the reporting of observational research studies (Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] statement), but this is less widely enforced across the dermatology publishing landscape.

The editors of medical journals also need to be more willing to publish important "negative" findings. However, achieving this goal is likely to be difficult, and the recent move of the European Medicines Agency to make all clinical study reports publicly available when submitted for drug approval is, therefore, another welcome step forward. This advance is supplemented by the Food and Drug Administration's archive of unpublished clinical studies (Turner, 2013). Having databases dedicated to randomized controlled trials for one specific disease, where all clinical trial data can be easily searched, such as the Global Resource for Eczema Trials database (www.greatdatabase.org.uk), is also a useful addition. This resource was employed by Wilkes et al. (2016) for their systematic review.

Furthermore, comparability between studies requires international consensus on core outcomes sets. For atopic eczema, this was addressed by the Harmonising Outcome Measures for Eczema group (<http://www.nottingham.ac.uk/homeforeczema/index.aspx>), and similar projects are now underway for psoriasis, vitiligo, and hidradenitis suppurativa, under the umbrella of the Core Outcome Measures in Effectiveness Trials initiative (www.cometinitiative.org).

Patient involvement has also become an integral part of these consensus finding projects to ensure that chosen outcomes are relevant, not only for physicians but also for those with the disease in question. The same applies to the prioritization of research funding efforts and the design and conduct of the research itself. Here, the UK National Institute of Health has led the way through funding of research prioritization projects on specific disease areas (www.jla.nihr.ac.uk) and the

active promotion of public involvement in research (www.invo.org.uk). However, such efforts will only bear fruit if they are adopted elsewhere, and concerted international effort will still be required to reduce waste in dermatology research, ultimately for the benefit of our patients.

Disclaimer

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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See related article on pg 2030

New Insights into the Molecular Distinction of Dysplastic Nevus and Common Melanocytic Nevus—Highlighting the Keratinocyte-Melanocyte Relationship

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Mitsui et al. approach the problem of differentiating dysplastic nevus from common melanocytic nevus through a molecular lens. Whereas most of the literature on this topic shines the spotlight toward melanocytes, the focus of this paper is shifted to the tumor microenvironment. Using microarrays, reverse transcriptase-PCR, and immunohistochemistry, their results emphasize the role of keratinocyte dysplasia within dysplastic nevus.

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The concept that dysplastic nevus (DN) are at an intermediate step between common melanocytic nevus (CMN) and melanoma was first put forth by Clark et al. (1978), a concept that has been fraught with contention ever since. The uncertainty regarding DN is twofold. First, ambiguity surrounding the hierarchy of melanocytic tumors results, at least in part, from the histological challenge of differentiating DN from CMN. Second, disagreement exists over the inherent risk of DN to progress to melanoma and how this relates to their role as a risk factor for melanoma. In 2016, nearly four decades later, the field of dermatology still lacks a clear consensus on these matters. Mitsui et al. (2016) in a paper titled “Discrimination of dysplastic nevus from common melanocytic nevus by cellular and molecular criteria” describe differences between DN and CMN, thereby shedding new light on the mechanistic etiology of DN.

The clinical relevance of DN relates to their proposed characterization as premalignant melanocytic lesions that are associated with increased lifetime risk of becoming melanomas. Their clinical significance is variable, depending on the ability of physicians to distinguish DN from CMN. Historically, DN have been identified by a constellation of clinical and histological features, although several studies have demonstrated low correlations between clinical atypia and histologic dysplasia with respect to the identity of melanocytic lesions (Duffy and Grossman, 2012a). The World Health Organization weighed in on this question in 1991, when it defined DN solely on their histologic features, whereas the National Institutes of Health defined them clinically in 1992 (Rosendahl et al., 2015). Although consensus has not been reached on methods of separating DN and CMN into distinct entities, studies of the molecular and genetic differences between the two suggest DN do, indeed, have distinguishing features. Mitsui et al. (2016) provide further insight into this question, insight that helps to define molecular features of DN.

The current literature is divided when it comes to distinguishing histologically diagnosed DN from CMN using molecular and genetic characteristics;

