Democratizing the Clinical Trials Agenda in Dermatology

Randomized controlled clinical trials (RCTs) occupy a pivotal position in assessing the effectiveness of treatments for skin disease. The rudiments of the experimental design allow for control of selection, performance, detection, and attrition bias, and prospective trial registration offers further protection against selective reporting outcome bias and publication bias (Williams and Dellavalle, 2012). Clinical trials are the backbone of systematic reviews of clinical interventions, treatment guidelines, and drug licensing submissions. Cost-effectiveness studies in relation to RCTs are also essential for informing commissioning decisions in countries with state-funded health care, such as those undertaken by the UK National Institute of Health and Clinical Excellence. Despite their potential in reducing treatment uncertainties in dermatology, the usefulness of RCTs is limited by two factors: (i) the quality of design and reporting and (ii) the clinical question that the trials address.

Although there are some sparkling diamonds (Green *et al.,* 1999; Joly *et al.,* 2009), clinical trials in dermatology are often too small, poorly designed, and too poorly reported to reduce treatment uncertainties (Nankervis *et al.,* 2012). The problem of poor trial reporting is potentially easy to fix by requiring all trials to report the essential trial features as specified in the CONSORT-2010 statement (http://www.consort-statement.org), as is the policy of the *Journal of Investigative Dermatology* (Williams and Goldsmith, 2006). Selective reporting outcome bias (choosing which results of many to highlight once the study has been analyzed) can be overcome by prospectively registering all RCTs in a publicly accessible database before recruitment starts (Chan *et al.,* 2004). Small trials are trickier to address. Time and time again, when systematic reviews of skin disease treatments are prepared by the Cochrane Collaboration, the same predictable results emerge—around 30 underpowered and highly heterogeneous RCTs, most of which are at high risk of bias because of unclear description of key elements such as randomization, blinding, and loss to follow-up (Whitton *et al.,* 2010; van Zuuren *et al.,* 2011). Typically, these reviews end up with that frustrating conclusion "insufficient evidence" or that vacuous phrase "more research is needed," which, although true, is of little use to clinicians. More research of the same type is *not* needed—what is needed is *less* but *better* research in the sense that the proposed RCT will answer a key dilemma in dermatological clinical practice, is large enough to answer the questions posed, and is reported clearly enough to allow the reader to decide whether the trial was a good one (Williams, 2011).

Improving study design and reporting can be overcome to some extent by these measures, but how can the clinical trials agenda for dermatology better reflect clinical priorities? It is no use relying on the drug industry to produce a comprehensive plan to solving all treatment dilemmas in dermatology (Naldi *et al.*, 2010). The drug industry has its own agenda of trying to produce new, effective, and safe treatments that will also result in financial return. There is nothing wrong with that, apart from the fact that, like any other business, the industry agenda is guided by the need to offer something that is better than existing treatment in diseases that are common enough to ensure returns on investment. It is also worth noting that trials run by industry are generally well designed and well reported (Thomas *et al.,* 2008) and are a standard to which independent research should aspire. Industry cannot be relied on to answer key questions in dermatology such as "How does this new treatment compare to existing treatments?" as opposed to "Does this treatment work when compared with placebo and is it reasonably safe in the short-term?" A paucity of comparative-effectiveness research (according to the Agency

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for Healthcare Research and Quality, http://www.effectivehealthcare.ahrq.gov/index.cfm/what-is-comparative-effectiveness-research1) has meant that the market has become flooded with more and more products, some of which offer genuine choice, but many of which are simply "me too" products of dubious advantage. In the UK, for example, we have over 20 different topical preparations for acne based on just five main ingredients (Joint Formulary Committee, *British National Formulary*, http://www.bnf.org/bnf/index.htm). How can any doctor decide which is best unless they have been tested against each other on a level playing field? Such comparative-effectiveness studies are rare, but when they are done, they can produce some surprises; for example, a study comparing five different acne regimens for mild facial acne in the community found that old-fashioned and cheap 5% benzoyl peroxide was just as effective as and had fewer adverse effects than oral minocycline (Ozolins *et al.,* 2004). Another study of systemic therapies or phototherapy for psoriasis has shown that effectiveness in a real-world clinic setting is lower than that reported in previous trials (Gelfand *et al.,* 2012). The lack of symmetry in the tree of dermatology clinical trials research (Figure 1) also percolates through to evidence-based guidelines. Those producing them often find themselves in a dilemma of strongly recommending expensive new products developed by industry because they have passed the "RCTs level of evidence" test, at the expense of older but very-well-established products (Gilchrest and Martin, 2012), a mismatch I call the inverse research law—where the need for evidence is greatest, the quality and quantity of evidence are least.

In addition to addressing comparative-effectiveness research for common skin problems, the second challenge for the dermatology clinical trials agenda is how to address the many questions that need answering about less common skin diseases such as pyoderma gangrenosum (Craig *et al.,* 2012) or questions that address the use of established cheaper treatments such as oral tetracyclines for bullous pemphigoid (Bratton *et al.,* 2012)—questions that are of high interest to the global clinical community but offer poor returns for industry. The same applies to nonpharmacological interventions such as water softeners or specialized clothing or bandages for atopic dermatitis or gloves for prevention of occupational hand dermatitis (Thomas *et al.,* 2011; Bauer *et al.,* 2010). Independent government and charity funding is needed to address such real-world comparative-effectiveness studies. Such sources do exist, but tapping into them is highly competitive—only applications of the highest perceived priority and quality are funded and only those that are supported by the right methodological and trial management expertise.

One way forward to tackle the many important questions that need addressing in clinical practice is to form a network of like-minded people. Such networks can be disease specific, for example, for autoimmune blistering diseases (Meyer *et al.,* 2011), or country-specific, as in the case of the UK Dermatology Clinical Trials Network (UK DCTN (http://www.ukdctn.org); Layfield *et al.,* 2011). The main function of the UK DCTN, which has been running for 10 years, is to identify and prioritize research questions and then to develop these questions into fundable proposals by undertaking feasibility studies and working with patients and clinical trial methodologists. Currently, the UK DCTN is running four national trials and has succeeded in competing for funds against the top medical and surgical specialties. In addition to developing and running clinical trials proposed by its membership, the network has also fulfilled a key educational role in bringing on trainees. Such trainees learn about topic prioritization exercises that are held between professionals and patients, trial development and funding application processes, and, later, the management and successful delivery of funded trials. But perhaps the greatest value of such a network is the way in which it engages the clinical dermatology community. Previous dermatological clinical trials have largely been the domain of academics—and rightly so because research is what academics do. Yet many busy clinicians also yearn to participate in, rather than lead, clinical research—clinicians who might have done substantial research during their training, but who now find themselves overwhelmed by clinical practice. Networks such as the UK DCTN have tapped into the enthusiasm of such clinicians in a way that has enabled much wider engagement with identifying and reducing clinical uncertainties in what may be described as a "democratization of clinical research" (Lloyd and White, 2011). Clinicians are often in the best position to suggest important questions for investigator-initiated research. Indeed, it was such a clinician—the late Neil Cox—who suggested the first two UK DCTN trials on prevention of cellulitis relapses with oral penicillin, the results of which are now delivering benefit back in the clinic (Thomas *et al.,* 2012). The UK has also been fortunate in recent years to have the benefit of an integrated network of research nurses funded by the National Institute for Health Research Comprehensive Clinical Research Network (http://www.crncc.nihr.ac.uk/about_us/ccrn/specialty/dermatology) who are dedicated to recruiting into national portfolio studies, thereby helping with study delivery.

This example of the UK DCTN is not intended to serve as a blueprint for all countries to follow, but is an example of what is possible when the clinical and research communities collaborate across many centers to compete for national funding against other medical specialties. Skin disease has many trump cards to play when making the case for funding, such as

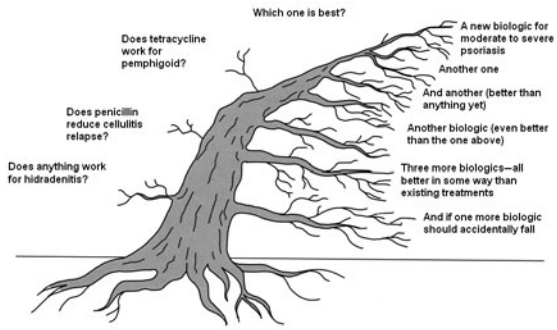

Figure 1. Investigator-led comparative-effectiveness research questions. Such questions are still twigs in the overall agenda depicted in the tree of dermatologic clinical trials.

high prevalence or large impacts on quality of life (Schofield *et al.,* 2009). Administrative hurdles for approvals within and across countries can be extremely challenging, but they can be overcome and are easier to manage with dedicated core staff. There is a real opportunity for other countries and groups to organize themselves into professional networks that work to industry standards and are able to tap into what limited funds are available (Sivanandam *et al.,* 2010). There is great potential for international collaboration in such an endeavor. To this end, the International Federation of Dermatology Clinical Trial Networks (http://www.ifdctn.org) has been set up to share good practices. Trial protocols can be shared so that robust designs can be adapted when evaluating similar questions in different populations emanating from different countries. Other countries may choose to evaluate the same drugs in different populations or use different standard comparators based on availability and local priorities. Research wastage could be reduced by minimizing unplanned duplication of trials. Such a federation will also encourage the use of the same outcome sets (Schmitt *et al*., 2011) for particular diseases to facilitate future network meta-analysis and comparisons in systematic reviews and guidelines. The ultimate potential for such an international federation is to work together on reducing uncertainties for rare skin diseases, such as looking at the possible benefits and harms of immunoglobulin for toxic epidermal necrolysis (Walsh and Creamer, 2012).

There has never been a more exciting time for comparative-effectiveness research in dermatology, but progress can be achieved only by teaming up with methodologists and by working together within and across countries. Some organizations, such as the American Dermato-Epidemiology Network (http://www.adenet.us/DECTRC.html), have already made a start in the right direction. The *Journal of Investigative Dermatology* is proud to be part of this journey of global unity in improving the relevance and quality of dermatology clinical trials and welcomes high-quality clinical trial submissions that will make a difference in the lives of our patients.

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CONFLICT OF INTEREST

The author founded and now chairs the UK Dermatology Clinical Trials Network.

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