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Developing a Dermatology Clinical Trials Network for Improved Therapeutics and Clinical Outcomes Research

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Abstract The UK Dermatology Clinical Trials Network (UK DCTN) was set up to develop and conduct independently funded, high-quality randomised controlled clinical trials in skin disease. A number of trials are now complete, with others in recruitment or development. A clearly defined pathway for trial development is followed; a prioritisation panel initially assesses the trial followed by further scrutiny and development advice from the Network Steering Group. The remit of the network has expanded to include James Lind Alliance research priority setting partnerships and building research capacity through training schemes and pump-priming awards. Global initiatives are also now underway including the International Federation of Dermatology Clinical Trial Networks (IFDCTN) to share knowledge and good practice and conduct trials in very rare conditions and the Harmonising Outcome Measures for Eczema (HOME) initiative which aims to agree on core outcome sets for eczema by global consensus.

Keywords Clinical trials network · Dermatology · Research capacity · Research prioritisation · International Federation of Dermatology Clinical Trial Networks

What is the UK Dermatology Clinical Trials Network?

The UK Dermatology Clinical Trials Network (UK DCTN) was set up in 2002 to conduct independent high-quality randomised controlled clinical trials (RCTs) of interventions for the treatment or prevention of skin disease. The network is open to anyone with an interest in finding out what really helps people with skin problems. Most members are dermatologists, the remainder being made up of general practitioners, nurses, methodologists and patients/carers.

How Does the UK DCTN work?

Transparent and fair decision-making processes are a crucial aspect of the UK DCTN which is embodied in our clearly defined pathway for trial development. Trial vignettes suggested by our devolved membership are initially assessed by a Trial Generation and Prioritisation Panel (TGPP) to determine whether the research question has been sufficiently developed and whether it is clinically important, timely and scientifically sound. If approved by the TGPP, the research team will be invited to present the vignette to the wider UK DCTN Steering Group. This progression from the TGPP to the Steering Group is usually an iterative process that includes support from the UK DCTN co-ordinating centre. The Steering Group is responsible for evaluating trial proposals and deciding which ideas are progressed further through the Network. It consists of approximately 30 members from across the UK including clinicians, nurses, methodologists and patients to reflect the membership, and is chaired by Professor Hywel Williams.

Oversight of the UK DCTN is provided by an executive group, who make decisions on the strategic direction and business of the network with input from the steering group. The co-ordinating centre is based within the Centre of Evidence Based Dermatology (www.nottingham.ac.uk/dermatology) at the University of Nottingham and is responsible for developing and managing the trial portfolio, network infrastructure, publicity and delivering all UK DCTN events.

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Further information about the UK DCTN can be found on the website (www.ukdctn.org).

What Has Changed Since the Inception of the UK DCTN?

The UK DCTN has adapted to reflect the changes in the research landscape in the UK over the past 10 years. When the UK DCTN was set up, there was very little in the way of infrastructure support for clinical research in the UK. Today, it is a very different picture, and the National Institute for Health Research (NIHR) Clinical Research Network (CRN) now plays a central role in supporting the delivery of UK DCTN trials by funding a national network of research nurses to recruit into approved CRN portfolio studies. The UK DCTN remit has widened to include the provision of pump-priming funds for pilot work and a number of training programmes to increase research capacity. The UK DCTN also operates a scheme to allow high-quality, independently funded trials to be 'adopted' onto the portfolio in order to enable more dermatology research to benefit from the wider network membership.

What Has the UK DCTN Delivered?

Recently Published Trials

The PATCH Trials

The PATCH I and PATCH II trials (funded by Action Medical Research and the BUPA Foundation, respectively) are two closely related RCTs investigating whether penicillin (250 mg b.d.) could prevent repeat episodes of cellulitis of the leg compared to placebo. These trials were run by the UK DCTN and took place in 29 hospitals throughout the UK. A total of 274 patients took part in PATCH I and 123 patients in PATCH II. PATCH I (12 months of penicillin) included patients who had had at least two episodes of leg cellulitis in the last 3 years, whereas PATCH II (6 months of penicillin) recruited mainly patients who have had only one episode of cellulitis. In both trials, patients were followed for up to 3 years.

Both PATCH trials showed that penicillin taken after an episode of cellulitis reduced the number of repeat episodes. PATCH I results published in the *New England Journal of Medicine* [1••] showed that patients in the penicillin group were less likely to have another attack of cellulitis compared with the placebo group (22 % compared with 37 %). Although the evidence was not so strong in the smaller PATCH II study [2•], it showed a similar reduction in the number of repeat episodes of cellulitis in the group that received the penicillin.

However, there were some differences in the findings of the two trials. In PATCH I, protection was gradually lost after the 12 months of penicillin had stopped, suggesting that longer-term antibiotics may be required. But PATCH II results suggested that the preventative effect continued after the 6 months of penicillin had stopped; 20 % of the participants in the penicillin group had at least one repeat episode over the 3 years compared to 33 % of those who received placebo.

The two trials have been subsequently included in a systematic review of prevention of cellulitis recurrences which concluded that antibiotic prophylaxis can prevent recurrent cellulitis [3•]. It has also been shown that on balance, prophylactic penicillin is a cost effective intervention [4].

The SINS Trial

The SINS trial, funded by Cancer Research UK, was 'adopted' on to the UK DCTN portfolio and compared topical imiquimod with excisional surgery for low-risk basal cell carcinoma in 501 patients. Results published in *Lancet Oncology* at 3 years showed that only 84 % of patients in the imiquimod group were treated successfully compared with 98 % in the surgery group (RR 0.84, 98 % CI 0.78–0.91; $p<0.0001$) [5•]. Because imiquimod was inferior to surgery according to the predefined non-inferiority criterion, excisional surgery remains the gold standard for low-risk basal cell carcinoma. This precise estimate provides a clear evidence for health policy makers.

Recently Completed Trials in Rare Conditions

The UK DCTN has recently successfully completed two trials in rare skin conditions (STOP-GAP and BLISTER). These trials were made possible by working collaboratively as a trials network with more than 50 recruiting centres taking part to recruit the patient numbers needed.

The STOP-GAP Trial

The STOP-GAP trial was funded as part of an NIHR Programme Grant for Applied Research to compare systemic therapies for treating pyoderma gangrenosum, a rare painful and mutilating ulcerative condition [6]. This trial tested the hypothesis that ciclosporin is more effective than prednisolone. This was the largest trial of pyoderma gangrenosum ever conducted in which a total of 121 patients were recruited (against a target of 140). Results of this trial have been submitted for publication and will be available in 2015.

The BLISTER Trial

This trial was funded by the NIHR Health Technology Assessment Programme (HTA) and is an RCT comparing the safety and effectiveness of doxycycline with oral steroids (prednisolone) for the initial treatment of bullous pemphigoid

(a rare blistering skin disease of the elderly). The question for this trial was generated from a previous Cochrane systematic review [7, 8]. Both interventions are low cost and frequently used, yet they have never been compared properly—an example of the sort of study that is clinically important but one which would never be done by the pharmaceutical industry. The study uses a non-inferiority design which tests whether some loss of short-term effectiveness for doxycycline is outweighed by a reduction in longer-term side effects, which is a major concern of using oral steroids in this elderly population. The study has recently completed recruiting 258 patients (against a target of 256) across the UK and Germany, and data analysis is underway.

Trials Currently Recruiting

The CLOTHES Trial

This trial is designed to assess the effectiveness and cost-effectiveness of silk therapeutic clothing for the long-term management of eczema in children with moderate and severe eczema. Funded by the NIHR HTA, the trial aims to recruit 300 children with eczema aged between 1 and 15 years of age. Children will be allocated to receive standard care plus silk therapeutic clothing or standard care alone. The trial started recruiting in October 2013 and will continue until May 2015 with individual participation lasting 8 months (http://www.nottingham.ac.uk/research/groups/cebd/projects/clothes/index.aspx).

The BEEP Trial

The Barrier Enhancement for Eczema Prevention (BEEP) trial, also funded by the NIHR HTA Programme, will investigate whether applying emollients for the first year of life can prevent eczema from developing. The results of the recently published BEEP pilot study were encouraging [9••] and have informed the design of this large national definitive trial. Approximately 1300 newborn babies with a family history of atopy will be recruited over a 2-year period across approximately ten recruiting centres across the UK starting November 2014. The primary outcome is the proportion of infants with eczema at 2 years. Secondary outcomes include severity of eczema, time to onset, prevalence of other allergies, adverse reactions, quality of life and cost-effectiveness. The children will be followed up until their 5th birthday to look at longer-term effects of the intervention.

The hELP Trial

This trial funded by an NIHR Clinical Doctoral Fellowship aims to assess the best treatments for vulval erosive lichen planus in patients who have not responded to first-line therapy. Erosive lichen planus is a painful inflammatory condition affecting the vulva. This open label trial will compare the addition of hydroxychloroquine, methotrexate, mycophenolate mofetil or oral prednisolone to standard topical treatment. It is open to recruitment in ten centres across the UK until mid 2015.

The Hi-LIGHT Trial

Following on from the recent pilot trial [10•], the Hi-Light main trial will assess the possible benefits of hand-held narrowband ultraviolet light devices for people with early localised vitiligo. The trial, funded by the NIHR HTA, aims to recruit 440 participants, aged 5 years and above, with recent onset or actively spreading vitiligo and recruitment is due to start in early 2015.

Supporting Research Prioritisation

Priority Setting Partnerships

The UK DCTN supports a number of James Lind Alliance Priority Setting Partnerships (PSPs) which bring patients and health-care professionals together to identify uncertainties about the effects of treatments and to agree on a list of research priorities in a specific disease (http://www.lindalliance.org/). A PSP for vitiligo was conducted in 2011 [11], the results of which led to a commissioned call by the NIHR HTA and the recently funded Hi-Light trial. The UK DCTN has continued working with researchers on PSPs in eczema [12••], acne and hidradenitis suppurativa.

Pump-Priming Awards

Each year, the UK DCTN offers a pump-priming award of up to £10,000. This open competition themed call is usually linked to the Annual Evidence Based Update Meetings [13, 14] to reflect an area of interest already prioritised by the dermatology community. The purpose of the award is to pump-prime projects that will lead to an RCT being conducted through the UK DCTN. Previous awards have been made for research into the themes of acne, vitiligo and skin surgery.

Increasing Research Capacity

Fellowships and Awards

The annual educational research fellowships and awards are available to Specialist Registrars (SpR's) nurses, specialty and associate specialist (SAS) doctors and general practitioners (GP's). These competitive awards comprise a modest stipend which supports the award holders to attend a range of educational research activities including an evidence-based

dermatology course, critical appraisal skills workshop and the UK DCTN Steering Group meetings. Awardees also join a trial development team or carrying out other relevant research activity such as a Cochrane systematic review. Alumni of these fellowship awards typically remain integral members of the Network and have gone on to become clinical lecturers, research fellows and clinical leads on large RCTs, illustrating the return on the investments in these awards.

Trainees Group

It was recognised that more could be done to offer training in clinical trial design to trainee dermatologists who often recruit patients into UK DCTN trials. The bi-annual 'Trainee Group' was launched to meet this need and is centred around a 1-day interactive workshop. Several months prior to the workshop, delegates are allocated into working groups of approximately six dermatology trainees to develop a vignette for a clinical trial and conduct any pilot work required such as an audit of local practice. Groups are encouraged to work on projects that will give them publication opportunities, such as Critically Appraised Topics (CATs), within a relevant timescale for trainees. Each group is assigned two mentors from within the network membership who are experienced in the design and conduct of clinical trials. The first part of the workshop comprises presentations on critical appraisal skills and clinical trial design. During the second part, each group presents their vignette, and this is followed by discussion and constructive feedback. Good quality proposals with a dedicated trainee group are then taken through the standard UK DCTN processes, with the support of the group mentors, thereby contributing to the pipeline of clinical trials in development.

Global Network Initiatives

International Federation of Dermatology Clinical Trial Networks

The UK DCTN was initially set up to deliver trials in the UK but has since expanded to share its experiences with colleagues from other countries with view to stimulating the formation of a global network. The International Federation of Dermatology Clinical Trial Networks (IFDCTN) aims to connect researchers from around the globe, to share knowledge and good practice in doing independent dermatology clinical trials, to improve the quality of design and reporting of dermatology clinical trials and to eventually leading to collaborations on clinical trials of rare skin diseases that require a multi-country approach. The IFDCTN is currently based around a website repository of information such as international contacts, trial design toolkits, examplar trial protocols and existing networks, and will be developed further over time to include collaborative trials on very rare skin diseases.

Harmonising Outcome Measures for Eczema

The high number of trials conducted by the UK DCTN into the prevention and treatment of eczema is reflective of the significant burden of this common skin condition. Many different scales and instruments of varying quality have been used to assess the effectiveness of interventions in published eczema treatment trials making any form of comparison of the evidence such as a meta-analysis difficult [15]. The aim of the Harmonising Outcome Measures for Eczema (HOME) initiative is to agree on a set of core outcomes that will be measured and reported in all future eczema clinical trials (http://homeforeczema.org/). Consensus is achieved using an open and transparent process which includes systematically reviewing the instruments and their measurement properties, carrying out further research and/or validation studies if required and face-to-face consensus meetings [16••]. The HOME initiative includes researchers and patients interested in eczema from all over the world, and this global approach is vital to achieve true consensus.

The core outcomes for eczema trials will include the domains of clinician-reported signs, patient-reported symptoms, long-term control and quality of life [17]. The Eczema Area and Severity Index (EASI) was agreed as the preferred instrument to measure clinician-reported signs in all future eczema trials [18••], and the process for agreeing on the core outcome measure of the remaining three domains is underway. Other outcome measures can be included as required in addition to the core outcomes.

Challenges Facing the UK DCTN

The UK DCTN offers many benefits to the dermatology research community. The inclusive and collaborative nature of the network means that many dermatologists and dermatology nurses are able to participate and recruit into the UK DCTN trials. This recruitment across many settings also has the added benefit of increasing the generalizability of the results. However, although most dermatology care in the UK is delivered in primary care, the majority of UK DCTN members are dermatologists working in secondary care, so increasing members in primary care is an important goal for the network. The UK DCTN is actively encouraging more trials in primary care and has adopted the primary care-based CREAM trial, funded by the NIHR HTA, which is exploring whether oral or topical antibiotics in addition to topical corticosteroids improves disease control in children with infected eczema.

One of the major challenges in the early phase of developing a network is maintaining the enthusiasm of members during the several years it takes to get from inception of a trial idea through to publishing the results of the first trial. Being as inclusive as possible and opening up lots of recruiting centres for early trials and ensuring that there are several projects to choose have been key aspects that have helped to retain

interest and momentum within the UK DCTN. As the number of trials being taken on by the network increases, it is important to ensure there are a variety of trials on the portfolio so that different members are motivated to get involved. A mixed portfolio of trials that include short and long-term studies, different disease areas and a mixture of device, drug and surgical trials is desirable. Trials into rare diseases or particularly large trials often require recruitment to continue for several years. Such trials require perseverance and dedication of network members at recruiting centres which requires good structures, collaborative principles, communication and a sense of collective working for the greater good.

Some form of funded infrastructure is essential to drive a network like the UK DCTN. In addition to the many clinicians and academics working with the UK DCTN in various capacities, the UK DCTN is supported by three part-time-funded posts; a network manager, a trials development manager and an administrator and funding is included in new trial grant proposals in order to sustain the network.

Summary and Conclusions

The UK DCTN is an active collaborative network with a focus on delivering high-quality clinical trials in dermatology. To sustain this in the longer-term, the remit of the network also includes providing training to future researchers, supporting the development of dermatology research through pump-priming awards and priority setting partnerships and through global initiatives to address issues that require a worldwide approach including trials into rare conditions and core outcome sets.

Compliance with Ethics Guidelines

Conflict of Interest Joanne R. Chalmers, Carron Layfield and Hywel C. Williams declare that they have no conflict of interest. Hywel Williams is the Chair of the UK DCTN and Carron Layfield and Joanne Chalmers are part of the UK DCTN co-ordinating team.

Human and Animal Rights and Informed Consent All studies by Hywel C. Williams involving animal and/or human subjects were performed after approval by the appropriate institutional review boards. When required, written informed consent was obtained from all participants.

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