Research Update

CLINICAL INVESTIGATION

The UK Dermatology Clinical Trials Network: how far have we come?

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The UK Dermatology Clinical Trials Network (UK DCTN) was established in 2002 to fill a gap for independent evidence for the treatment and prevention of skin disease. The network has now grown into a UK-wide collaborative group of over 750 members and has completed five multicenter independent clinical trials with a further four new studies in set-up. This article describes how the UK Dermatology Clinical Trials Network has advanced since our original article in Clinical Investigation in 2010, which outlined how the Network was established. By sharing the development and results of our studies, and other initiatives such as our trainee Fellowships and Priority Setting Partnerships, we hope to stimulate the formation of other similar collaborative clinical research networks.

Keywords: clinical trials • dermatology • independent • network • research

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Established in 2002 with just 20 members, the UK Dermatology Clinical Trials Network (UK DCTN) has grown to a collaborative group of over 750 dermatologists, nurses, primary care staff, healthcare researchers and patients/carers across the UK in 2013. Membership of the UK DCTN is free and open to anyone with an interest in applied dermatology research. The steady increase in membership and active participation in our trials is testament to the genuine and growing interest of the UK dermatology community in contributing to high-quality independent clinical research.

The aim of the network is simple – to develop high-quality randomized-controlled clinical trials (RCTs) of interventions for the treatment or prevention of skin disease. Priority is given to trials that address questions of importance to health care professionals, patients and the UK NHS. The Network is open to trial suggestions from any of its UK and Eire based members; these are then prioritized and developed using a rigorous and predefined trial development process [1]. Funding for individual trials arises from external grant applications made to the National Institute of Health Research (NIHR) and charitable bodies. The network works closely with the NIHR Dermatology Specialty Group [2] who provide a national infrastructure of dedicated research nurses to deliver its studies.

The UK DCTN is run by an Executive Group with an independent Chair and a Steering Group consisting of approximately 30 members, which is chaired by Professor Hywel Williams (University of Nottingham, Nottingham, UK). The Steering Group is responsible for evaluating trial proposals and deciding which ideas are developed further through the network. The ideas considered by this group have been prioritized by our Trial Generation and Prioritization Panel. The role of the UK DCTN coordinating center, which is based within the Centre of Evidence Based Dermatology (University of Nottingham) [3], is to develop and manage the network's portfolio of clinical trials and to develop the network as an organization. Further information about the background to the UK DCTN can be found on its website [4].

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Completed studies

Four RCTs have now been completed, all of which have resulted in high-profile publications [5–7], with others in preparation. The results from two of these studies evaluating the use of prophylactic antibiotics for the treatment of cellulitis at home (the PATCH studies) are outlined below.

The PATCH studies

The PATCH I and PATCH II studies (funded by Action Medical Research and the BUPA Foundation, respectively) are two closely related RCTs investigating the long-term use of low-dose penicillin to prevent further episodes of cellulitis of the leg (a painful and common skin infection) [8]. Both the PATCH I [5] and PATCH II [6] trials showed that taking low-dose penicillin after an episode of cellulitis reduced the number of repeat episodes. However, there were some differences in the findings of the two trials.

PATCH I was designed to test if low-dose penicillin (250 mg) taken twice a day for 12 months could prevent further attacks in patients who suffer from repeat episodes of leg cellulitis. Patients who had had at least two episodes of leg cellulitis in the last 3 years were included in this trial. PATCH II was almost identical to PATCH I, but this trial evaluated just 6 months of low-dose penicillin (250 mg) taken twice a day, and recruited mainly patients who had only one episode of cellulitis. In both PATCH I and II, patients remained in the trial for up to 3 years to see whether or not the penicillin was effective only whilst it was being taken, or whether there were longer term benefits after the antibiotics had been stopped. These trials took place in 29 hospitals throughout the UK and Eire. In total, 274 patients took part in PATCH I, and 123 patients took part in PATCH II.

The PATCH I trial found that patients in the penicillin group were less likely to have another attack of cellulitis compared with the placebo group (22 vs 37%, respectively) whilst taking the medication. However, this protection was then gradually lost after patients stopped taking the medication after 12 months, suggesting that longer-term antibiotics may be required in patients with recurrent cellulitis to prevent further episodes.

Although the evidence was not so strong in the smaller PATCH II study, it showed a similar reduction in the number of repeat episodes of cellulitis in the group that received the penicillin whilst taking the medication. However, unlike PATCH I, this trial suggested that the preventative effect continued after the medication had stopped at 6 months. Overall, 20% of the participants who took penicillin had at least one repeat episode over the 3 years compared with 33% of those who received placebo tablets.

Cellulitis of the leg is extremely common, causes a lot of distress to patients, and results in time off work or other daily activities. By demonstrating that a simple, low-cost and safe intervention such as low-dose penicillin taken for 6–12 months can reduce the number of repeat episodes, these trials could improve the lives of many thousands of patients, and also potentially reduce costs to the NHS by reducing hospital admissions.

Other recently completed studies

BLISTER

This study, funded the NIHR Health Technology Assessment (HTA), is an RCT comparing the safety and effectiveness of doxycycline with oral steroids (prednisolone) for the treatment of bullous pemphigoid (a rare blistering skin disease of the elderly). The study uses a noninferiority design that tests whether some loss of short-term efficacy is outweighed by longer term side effects, which is a major concern of using oral steroids in this elderly population. The study has recently completed recruitment of 258 patients (against a target of 256) across the UK and Germany with patients still in follow up for 1 year. This fantastic achievement is due to the dedication and perseverance of UK DCTN members who have managed to keep recruitment going for a 3-year period, demonstrating that it s possible to undertake large trials in less common diseases in dermatology, when good collaborative principles and structures are in place [9].

STOP GAP

This study, funded by a contribution from a NIHR program grant, tests the hypothesis that ciclosporin is more effective than prednisolone for the systemic therapy of pyoderma gangrenosum (a rare painful and mutilating ulcerative condition). There are two parts to the trial – an RCT comparing the two systemic therapies and an observational study for patients who were only deemed to need topical therapy [10]. A total of 188 patients have been recruited; 121 into the RCT (against a target of 140) and 67 in the observational arm, making this the largest study of pyoderma gangrenosum ever conducted. This study also illustrates the benefits of working collectively in a rare disease area [11].

LIMIT 1

This smaller Phase II study funded by a grant from the NIHR Research for Patient Benefit Scheme was conducted to help determine whether imiquimod is a sufficiently effective treatment for lentigo maligna (a form of skin cancer). The study failed to provide convincing evidence of a signal to proceed to a full trial, illustrating the value of such external pilot RCTs before rushing into large-scale and costly national studies.

New studies

As shown in Table 1, the UK DCTN has been successful in securing over £8 million in independent funding over the last 10 years to support its prioritized studies. Some of our newly funded UK DCTN-led studies are outlined below. Other studies in our development pipeline cover a diverse range of skin diseases including skin cancer, acne, skin surgery, alopecia and vitiligo.

CLOTHES

This is an RCT designed to assess the possible effectiveness and cost–effectiveness of silk therapeutic clothing

Table 1. Summary of UK Dermatology Clinical Trials Network funded studies.

Study	Funding Source	Awarded	Amount (GB£)
Pilot studies to inform the design of a UK multicenter RCT of prophylactic antibiotics for the prevention of recurrent cellulitis of the leg	British Skin Foundation	July 2005	10,000
RCT to investigate whether prophylactic antibiotics can prevent further episodes of cellulitis (erysipelas) of the leg (PATCH II)	BUPA Foundation	June 2005	190,000
RCT to investigate whether prophylactic antibiotics can prevent further episodes of cellulitis (erysipelas) of the leg (PATCH I)	Action Medical Research	July 2005	120,000
RCT to compare the safety and effectiveness of doxycycline with prednisolone for initial treatment of bullous pemphigoid (BLISTER)	NIHR HTA Commissioned Call	April 2006	1,000,000 (including a project extension)
Pilot studies for a multicenter clinical trial studying topical and oral treatments for pyoderma gangrenosum patients (STOP-GAP)	British Skin Foundation	May 2007	10,000
Setting priorities and reducing uncertainties in the prevention and treatment of people with skin diseases (includes main STOP GAP RCT on pyoderma gangremosum)	NIHR Programme Grant	June 2007	1,950,000
Effect of topical imiquimod on lentigo maligna; a Phase II study (LIMIT I)	NIHR Research for Patient Benefit	July 2007	250,000
RCT to investigate the use of silk clothing to treat childhood eczema (CLOTHES)	NIHR HTA Commissioned Call	Sept 2012	1,000,000
A study to assess the best treatments for vulval erosive lichen planus when patients do not respond to first-line therapy (hELP)	NIHR Clinical Fellowship Scheme	June 2012	330,000
RCT to investigate whether applying emollients for the first year of life can prevent eczema in a high-risk population (BEEP)	NIHR special funding scheme for projects arising from NIHR Programme Grants	June 2013	1,940,000
RCT assessing hand-held narrowband UV devices, both alone and in combination with topical steroid, for early focal vitiligo (HI-LIGHT)	NIHR HTA Commissioned Call	July 2013	1,300,000
Total	–	–	8,100,000

HTA: Health Technology Assessment; NIHR: National Institute for Health Research; RCT: Randomized-controlled trials.

for the long-term management of eczema in children with moderate/severe eczema. Funded by the NIHR HTA the trial aims to recruit 300 children aged 1–15 years with eczema. 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 for 3 years with individual participation lasting 8 months [12].

HI-LIGHT

This stands for Home Interventions and Light therapy for the treatment of vitiligo (a skin condition that results in disfigurement due to loss of pigment from the skin, which is especially noticeable in dark-skinned people). This will be an RCT assessing the possible benefits of hand-held narrowband ultraviolet light devices, used either alone or in combination with topical steroids, for people with early localized vitiligo. The trial aims to recruit 440 participants, aged 5 years and above, with recent-onset or actively spreading vitiligo. Participants will be allocated to one of three groups:

- Home-based narrowband UVB delivered with hand-held units plus placebo ointment;
- Topical corticosteroid ointment plus a sham UV device;
- Combination treatment with narrowband UVB plus corticosteroid ointment.

The trial is due to start recruiting towards the end of 2014 with individual participation lasting 21 months (9 months of treatment and 12 months of follow up).

hELP

This study aims to assess the best treatments for vulval erosive lichen planus in patients who do not respond to first-line therapy [13]. Erosive lichen planus is a painful inflammatory condition affecting the vulva. The study is funded by an NIHR Clinical Doctoral Fellowship. The RCT is planned to start in May 2014 and will be a multicenter, four-armed, open-label study investigating the addition of hydroxychloroquine, methotrexate, mycophenolate mofetil or oral prednisolone to standard topical treatment. The study will recruit in ten centers across the UK.

BEEP

The BEEP RCT investigates whether applying emollients for the first year of life can prevent eczema from developing in the children as they grow older. This will be a large trial; approximately 1300 newborn babies with a family history of eczema, asthma or hay-fever will be recruited to the trial over a 2-year period in ten recruiting centers across the UK. The primary outcome is the proportion of infants with eczema at 2 years. Secondary outcomes include severity of eczema, time to onset, wheezing, adverse reactions, quality of life and cost–effectiveness. The children will then be followed up until their fifth birthday to look at longer term effects of the intervention, such as possible prevention of asthma.

Setting the research agenda: priority setting partnerships & the UK DCTN themed call

James Lind Alliance Priority Setting Partnerships (PSPs) identify and priorities treatment uncertainties that need to be addressed by further research. PSPs bring patients and healthcare professionals together to identify uncertainties about the effects of treatments and to agree a list of research priorities in a specific disease to inform the research agenda [14]. The collaborative approach leads to priorities that reflect both clinical and patient priorities and therefore should yield the greatest improvements in healthcare.

After conducting a successful priority setting exercise on vitiligo in 2011 [15], which led to a commissioned call by the NIHR HTA and the recently funded HI-LIGHT trial outlined above, the UK DCTN has continued working with researchers on PSPs on eczema [16], acne and hidradenitis suppurativa. We hope that identifying research priorities in this way will lead to better, more informed and needed research being carried out in these areas.

In 2012 the Network launched a themed call with an associated £10,000 development fund award. To date, two projects have been funded by this scheme, both investigating previously under-researched areas of skin disease – acne and vitiligo.

Developing research capacity

The UK DCTN recognizes the importance of building research capacity amongst healthcare professionals, which it achieves through a number of initiatives such as the UK DCTN Awards and by the formation of a UK DCTN Trainee Group.

The UK DCTN awards started in 2008, when the first UK DCTN Specialist Registrar Fellowship was established. Due to the popularity and success of this scheme it was subsequently expanded to encompass a range of clinical staff including general practitioners, nurses and staff/ associate specialist grade staff. All UK DCTN Awards are competitive, national awards that are made on an annual basis and are composed of £1500 to cover expenses for a range of educational research linked activities, including attending the British Epidermo-Epidemiology Society evidence-based dermatology course [17], critical appraisal tutorials with UK DCTN Chair Hywel Williams, attending UK DCTN Steering Committee meetings and joining a UK DCTN

Trial Development team or other relevant research activity. Specialist Registrar Fellow alumni have gone on to become clinical lecturers, research fellows and clinical leads on large RCTs, illustrating the potential returns on investments designed to facilitate interested individuals to become more actively engaged in research.

The Specialist Registrar Fellowships have been invaluable in forging links with the dermatology trainee community. Because involvement in UK DCTN-led studies has been such an excellent way for trainees to engage with clinical research, we have built on these foundations by establishing a UK DCTN Trainee Group to enable more dermatologists at the early stages of their career to become actively engaged in UK DCTN studies.

In April 2013 we held a clinical research skills training day to support this new group. The event covered critical appraisal skills and the development of research ideas for clinical trials. Prior to the event delegates were allocated into small working groups and assigned two mentors to assist them in developing an idea for a dermatology clinical trial, which was then presented on the day. Research topics included skin surgery, alopecia, vitiligo, skin cancer and scleroderma. A number of groups are continuing to develop these study ideas, which will benefit the UK DCTN by helping to maintain a healthy pipeline of clinical trials in development.

The international federation of dermatology clinical trial networks

Following on from the success of the UK DCTN, we have launched an international federation of dermatology clinical trial networks (IFDCTN). The aim of the IFDCTN is to bring together colleagues from around the globe, to share good practice in doing independent dermatology clinical trials, to improve the quality of design and reporting of dermatology clinical trials, and to eventually work together on undertaking clinical trials of rare skin diseases. We aim to achieve this through education, collaboration, sharing knowledge and network development.

Now in its initial stages, the IFDCTN is primarily a website repository for information such as international contacts, trial design toolkits, exemplar trial protocols and existing networks [18].

Future perspective

The future of the UK DCTN will always rely on the success of competitive funding and on dedicated teamwork and philosophy that democratizes the research agenda back to healthcare professionals on the front line, along with patients and carers [19]. Threats to the organization includes trial fatigue as each new national trial struggles to recruit into difficult trials – a potential problem largely overcome by including a diverse portfolio of trials that interests different groups of professionals and patients at different times. Although other research groups may try to compete with the UK DCTN for some trials, it is hoped that collaboration will be the key to progress given the vast amount of work that needs to be done. Succession planning by investment in training awards and trainee study development groups is also essential if the organization is to continue to grow and address the many uncertainties that need to be addressed for people with skin disease. The UK DCTN will never be in a position to address all the uncertainties for the 1000 or so skin diseases that exist, and it is hoped that encouraging the development of other similar country- or disease-specific networks across the world will help to map out and reduce the most important priorities for research that face our communities.

Disclaimer

The views expressed in this article are those of the authors and not necessarily those of the NHS, the National Institute of Health Research or the Department of Health.

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Executive summary

- The UK Dermatology Clinical Trials Network (UK DCTN) has demonstrated how a clear shared vision, good organization and management and hard work can play a world-leading role in reducing uncertainties in treating skin disease.
- The UK DCTN has grown steadily over the last 5 years into a vibrant community of healthcare professionals and patients that identifies, prioritizes and conducts large-scale randomized controlled clinical trials for people with skin diseases.
- The UK DCTN has also played a vital role in changing the culture of clinical research in UK dermatology away from University silos and into the clinical community where the research is needed most.
- The UK DCTN has invested in developing new researchers who in turn come back to the organization and contribute to its development.
- Its model serves as a template that dermatologists or clinicians in other countries could follow as part of a global initiative that avoids unnecessary duplication of work.

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