# INVESTIGATIO

## The Scottish Children's Research Network: challenges, opportunities and achievements

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Although research in children can be challenging for investigators, children and their families, it is only through well-designed and ethical studies that improvements in diagnosis, disease prevention and disease management can be made. The Scottish Children's Research Network (ScotCRN), which was established in 2006 with core funding from the Scottish Chief Scientist Office, combines the benefits of central coordination of adopted research, including clinical trials, with the advantages of practical infrastructure support at local investigator level. Close collaboration is maintained with the equivalent networks in the other three UK health administrations and with emerging equivalent networks across Europe. Access to clinical investigators and patient populations across the whole range of pediatric specialties and the young person's advisory group provide valuable resources for potential academic and industry partners. Encouraging pediatric clinicians to participate in research and providing practical support has resulted in a significant broadening of the pediatricand child-health research base and level of activity in Scotland. Future challenges will include maintaining this momentum and advocacy for the specific needs of children and families engaged in research.

Keywords: children • clinical trials • funding model • recruitment • research network

Clinical research and clinical trials in children offer particular challenges both to the investigator and to participating children and families. This results in the relative dearth of trials and evidence on the effective and safe use of medicines in children. Commercial considerations have also contributed to this unsatisfactory state of affairs, as children comprise 20% or less of the whole population, carry a lower burden of long-term chronic illness and express a number of rare, mainly congenital disorders that are not observed in the adult population [1]. Furthermore, conditions such as hypertension, peptic ulceration, depression and cancers have a much higher prevalence in adults, thereby reducing the financial incentives to perform clinical trials in children as the investment required may far exceed the potential revenue from subsequent product sales in this young age group. Additional expense may also arise when juvenile animal toxicology studies are required [1] and when special formulations, such as drops, suspensions or syrups, are needed, which require appropriate stability and palatability testing, together with due consideration to dental hygiene. Liquid formulations also require bulkier packaging and more storage space and several strengths may be required to accommodate the differences in pharmacokinetic and pharmacodynamic studies across the spectrum of childhood from infancy to adolescence. There are also ethical and practical difficulties involved in inclusion of children in all types of research, particularly for interventional studies such as clinical trials of medicines or new physical treatments.

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Children entering a clinical trial should have a reasonable chance of obtaining some direct benefit and, consequently, Phase I clinical studies on healthy child volunteers, with the exception of vaccines and other preventative measures, may not be considered ethical [2]. The child's understanding of the value of research may also be different from those of adults with a greater potential for distress even when employing techniques such as blood sampling that would be classified as minimal risk in adults. In most countries, children under the age of 16 years require proxy consent by a parent or legal guardian as they are not considered mature enough to provide their own fully informed and, hence, legally binding consent. There are some national exceptions to this approach, such as in the Scottish 1991 Age of Legal Capacity Act [101], which provides the opportunity for children of any age, who are judged to be competent to fully understand the consequences of proposed medical interventions, to give their own consent independent of their parents or legal guardians. Although research interventions including clinical trials are not specifically addressed in the Scottish Age of Legal Capacity Act, the Scottish Children's Research Network (Scot-CRN) has developed guidance for clinical researchers that is compatible with the 1991 act [102]. Apart from national variations in legislation and practice, it is accepted as good clinical practice, whatever the nationally defined legal age of capacity, that children should be given the opportunity to have the proposed study explained in age-appropriate language, together with the opportunity to participate in registering their agreement or 'assent'. In this context, informed consent or assent means that participating children are mature enough to fully understand the nature and consequences of their participation, have the right to withdraw at any time without prejudice to their treatment and that they have had the opportunity to discuss and ask questions with the research nurse, or designated lead investigator at that site. Challenges to the inclusion of children in research are not only related to the issues discussed above, but also to concerns and priorities of children's healthcare professionals who may have had very little experience in the conduct of research studies and, hence, a reluctance to consider and promote clinical trials and research in their patients [3].

Recognition of a lack of evidence and a relatively low level of research into medicines in children has resulted in major initiatives and legislation in the USA in 1999, and in the regulation on medicinal products for children in the European Union passed by the European Parliament in 2006 and enacted in early 2007 [103]. The European regulation requires pharmaceutical companies to

outline their plans for pediatric indications and conduct studies in children before being awarded a license for human use, unless a well-argued and agreed case for a waiver is accepted. In return, companies can expect an extension to their patent protection, which may result in significant return over investment in such pediatric programs [4]. However, the resultant increasing demand for clinical trials in children has not always been met by a willingness from hard-pressed clinicians to participate in such trials. For clinicians not previously involved in such research, the requirements for tightly regulated clinical research can appear daunting. Key requirements include the development of age-appropriate patient information material, making ethics committee applications and answering subsequent queries, negotiation with health service managers for the required infrastructure support and in the identification and explanation of the proposed research to patients and their parents and guardians. For some of the rare disorders observed in children, multicenter collaborations also need to be established. In this context, the UK National Health Service (NHS), the largest state-funded whole-population healthcare system in the world, has recognized its potential in supporting research across all age groups and specialties, including children [104]. Within the UK, the organization and delivery of healthcare through the NHS is the responsibility of the four devolved administrations and in Scotland, as in the other three administrations of England, Wales and Northern Ireland, support for clinical trials is embedded within the NHS [105]. In the context of the UK clinical research collaboration (UKCRC), the four devolved UK administrations have adopted strategies and provided core infrastructure funding in support of clinical trials and clinical research in children. The special needs of children was recognized in the establishment of the Scottish Medicines for Children Network in 2006 with subsequent extension of the research brief to all clinical research including non-medicine studies resulting in the relaunching of the network in 2009 as the ScotCRN [106].

#### ScotCRN initiation & core infrastructure

At the outset, a distributed model was implemented with core support being provided in the four main population centers, each containing strong research infrastructures, as well as clinical undergraduate and postgraduate training in pediatrics and child health; namely Aberdeen, Edinburgh, Glasgow and Dundee (Figure 1). In each of these centers, a senior pediatric research nurse was appointed with overall co-ordination provided through one of the centers, initially Aberdeen. Core central support included 1 day a week for a Pediatrician Network Director, a full-time Network Manager, as well as secretarial, pharmacy and laboratory support. A management The Scottish Children's Research Network Research Update

board was also established including two senior clinicians from each of the four main centers charged with the responsibility of developing a research strategy, managing Network resources and reporting progress on a 6-monthly basis to the sponsoring body, the Chief Scientist Office of the Scottish Government [107]. Funding support was through the Scottish NHS Research and Development budget and local lead clinicians and a research pediatric nurse were encouraged to establish and/or consolidate child-friendly clinical research facilities (CRFs) in each of the four foundation centers.

#### Subsequent development

After a review in 2009, the need to extend support to all pediatric clinical research studies conducted within the NHS was recognized with a modest uplift in core funding and re-alignment of infrastructure costs. These included modest sessional support for a designated senior clinician network 'champion' in each of the four centers and a data/web manager to track all adopted studies being conducted within the Network. It was recognized that although the majority of clinical research was likely to remain with the four main population and academic centers, access to core support should be extended

to all pediatric units in Scotland with the adoption of regionally based Network nodes aligned with the four pediatric postgraduate training deaneries (Figure 1). From its inception, ScotCRN has maintained close links with the equivalent Networks in the other three NHS administrations in the UK through the UK Clinical Research Collaboration [108].

#### Infrastructure

Child- and family-friendly CRFs have been established in each of the main children's hospitals within each of the four geographically distinct regions (Figure 1). In Aberdeen, Dundee and Edinburgh, the CRFs are managed by the regional ScotCRN research nurse with further capacity built locally from a variety of sources, including local NHS R&D funding, and recovery of costs from commercial and public-funded research studies. This has proved to be an effective funding model with the core-funded



Figure 1. The four regionally based Scottish Children's Research Network nodes, which are aligned with the four pediatric postgraduate training deaneries. North East, South East and West, and the four largest cities.

ScotCRN nurses providing line management mentoring and peer support to each team of regional children's research nurses. In Glasgow an alternative model has been adopted where the ScotCRN nurse is a member of the CRF team that reports to the Nurse Manager with responsibilities for both adult and pediatric CRFs.

ScotCRN nurses from each region meet every 6 weeks, with the network manager and pharmacist and have collectively produced standard operating procedures to ensure that all clinical procedures and assessments across sites within the network conform to good clinical practice and established quality criteria, examples of which are shown in Table 1. Additionally the network manager and lead nurses meet regularly with local trial managers and NHS R&D officers in order to liaise on local issues regarding funding and resources.

Although the strategies employed to increase nursing capacity have varied by region, all have been

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Table 1. Standardized operating procedures.		
Generic	Outcomes	Study specific
Obtaining informed consent	Measurement and recording of body weight	Taking a child's body temperature using a TempaDOT™
Withdrawal of informed consent	Measurement and recording of height	Assessment of atopic dermatitis in children using SCORAD
Reporting adverse events	Venous blood sample	An observational pain assessment tool
Use of electrical equipment	Capillary blood sample	Saliva collection for ECP levels
Preparation, maintenance, approval and review of standard operating procedures	Obtaining and recording BP and pulse	Sputum induction using Norditalia MO-03 nebulizer
Data protection	Measurement of spirometry	_
Storage of medicines in clinics	Allergen skin prick testing	_
Monitoring and recording of refrigerator and freezer temperatures	Saliva collection for DNA	-
Reporting adverse events	Measurement of pain	_
Pregnancy testing 12–16 years	Measurement of exhaled nitric oxide Capillary blood glucose	-
BP: Blood pressure; SCORAD: SCORing Atopic Dermatitis.		

developed to work alongside ScotCRN and local R&D funding to ensure cost recovery for nursing input and resulting in significant increases in both the number of supported studies (Table 2) and children recruited (Figure 2).

#### **Coordinating center**

Expressions of interest and trial feasibility requests are received directly from pharmaceutical companies, from the largest of the UK children's networks the Medicines for Children Research Network England (MCRN) or NHS Scotland National Research Services. Using the network team's knowledge of the local clinicians, specialist nurses and specialty clinical networks, ScotCRN seeks expressions of interest from the most appropriate teams and coordinates their responses. If Scottish sites are selected, the network can provide support in set up. Where no noted interest or a negative opinion is received, the reasons are communicated to the enquirer and to date have included:

Table 2. Scottish Children's Research Network-supported studies.			
Node	Active studies/trials by year		
	2010–2011	2011–2012	
North	8	10	
East	11	15	
South East	12	19	
West	21	19	

- No children with the rare disease in question currently being managed in Scotland;
- Unwillingness to enter children with that condition in the control arm of the proposed study;
- Comparator drug not current standard practice;
- Competing studies in the same population.

ScotCRN are also contacted by the MCRN (England) when ongoing trials require additional sites and when, if capacity allows, the network identifies suitable sites and assists in trial set up, as well as providing nursing support.

Study and trial adoption requests are received by the network director and manager. After coordinating the signing of the Confidential Disclosure Agreement by the relevant NHS Boards and after initial pharmacy, clinical and nurse review, requests are forwarded, with an offer of ScotCRN support in completing the feasibility and study set up, to the most appropriate potential Scottish investigator(s) for their opinion.

Once centers and local investigators have agreed to participate, ScotCRN ensures that all relevant permissions including ethical and local NHS R&D approvals are in place, together with the appropriate level of local/ regional support, target numbers of recruits and time lines. Studies and trials are then formally adopted and resources allocated for study/trial completion. The Scottish Children's Research Network Research Update

#### Investigator/study/trial support

After study initiation, recruitment is closely monitored by the lead research nurses in each region, as well as the network manager. If a study is not recruiting to target, it is reviewed and recruitment strategies are put in place, such as for a network-adopted asthma pharmacoepidemiology study of newly presenting children with asthma (Figure 3). In this particular study, although 11 sites agreed to recruit patients, review at month 6 revealed a fall in target numbers and delays in site initiation. Remedial action was taken including opening of additional sites resulting in a return to target recruitment. Another dip in recruitment in mid-2011 resulted in a successful approach to the Scottish Primary Care Network with the desired result and study completion on time on budget and on target (Figure 3). Subsequent collaboration with Scottish Primary Care Network has become a feature of research in children where the condition of interest is commonly managed in primary care [5].

#### Child/young people's involvement

A young person's group (YPG) consisting of 24 11–17-year olds invited through schools and specialist children's nurses was established in August 2011. The role of the group is to act as advocates for young people participating in research and, using a combination of core ScotCRN staff and external contributors, the YPG has received training in:

- Clinical trial design from Phase I to IV, including randomization, use of placebos, blinding, pediatric formulations and comparator medicines;
- Licensing of medicines from conception to market;
- The role of ethics committees;
- Legal requirements in Scotland with respect to the Age of Legal Capacity (Scotland) Act 1991.

Additionally, the YPG has used scenarios, workshops and open discussion to express views and comment on research guidance, information sheets and materials developed for children and young people participating in research.

The YPG has contributed to the UK National Research Ethics Service consultation on "Guidance on Information Sheets for Children Participating in Research", which has been collated as a joint response



Figure 2. Number of Scottish children recruited to Scottish Children's Research Network-adopted studies 2008–2012.

from ScotCRN YPG and MCRN YPGs in Liverpool, Manchester and Birmingham to the national UK research ethics service.

The group has commented on the guidance being produced by the UK Clinical Research Networks on transition clinics for teenagers in long-term studies and has provided feedback on the provision of access to learning tools designed for use in schools. Other valuable contributions have been made for children attending CRFs over prolonged periods, for managing the initial transition to adult care with the research team and the most appropriate environments for teenagers involved in clinical research. Other practical contributions have included advice on the development of an application delivered on smart phones and tablets for an early-intervention study in autism.



Figure 3. Recruitment to the PAGES asthma pharmacoepidemiology study demonstrating actual against target recruitment and the two Scottish Children's Research Network strategic interventions (arrows).

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#### International contributions

One of the objectives of the Paediatric Regulation (Regulation [EC] No 1901/2006) is to foster high-quality ethical research on medicinal products to be used in children through efficient internetwork and stakeholder collaboration across Europe and beyond [103]. To meet this objective, the European Medicines Agency has established the European Network of Paediatric Research Networks in European Medicines Agency (Enpr–EMA) [6]. ScotCRN has been accepted as a Category 1 (highest level) member of the Enpr–EMA as it meets the required standards in all six required criteria:

- Research experience and ability;
- Network organization and processes;
- Scientific competencies and ability to provide expert advice;
- Quality management;
- Training and educational capacity to build competences;
- Public involvement.

Using this forum, ScotCRN has contributed to the review of the impact of the 2006–2007 regulation on medicinal product for pediatric use and to the proposed revision of the European clinical trials directive as it applies to children.

#### **Future perspective**

Encouraging pediatric clinicians to participate in research and in providing practical support has resulted in a significant broadening of the pediatric and child health research base and level of activity within the NHS in Scotland in a similar way to that observed in England [7].

The network is now over 6-years old and the provision of core funding for the coordination center and the locality-based research nurses and clinical 'champions' combines the benefits of a single point of access for potential research partners and lead investigators with the ability to respond to local research demands and initiatives.

The establishment of Enpr–EMA provides all participating and recognized networks, including ScotCRN, with opportunities for collaboration across Europe and beyond, to influence European Union policies and legislation relevant to research in children, and to contribute to the evidence base on the safe and effective use of medicines and other health interventions in children.

Enabling young people's voices to be heard has much to offer [8] and the involvement of young people will continue to be central to the work of the network in promoting and supporting research in children.

#### Disclaimer

The views expressed here are those of the authors who have no affiliations or financial interests that could be construed as a conflict of interest.

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#### **Executive summary**

- Scottish Children's Research Network enables and encourages high-quality clinical research in and for children at a national level.
  Network objectives are met by the management of trials in clinical research facilities staffed by experienced pediatric research
- nurses and the provision of practical support in the set up and conduct of both clinical trials and research.
- Involvement of young people is proving invaluable in supporting and promoting research in children.
- Distributed infrastructure support with unobtrusive central coordination combines the benefits of harnessing local enthusiasm and expertise with a single point of contact for potential industry and academic partners.
- Modest secure core funding is required in order to establish an effective and sustainable national network such as Scottish Children's Research Network.

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