**NIHR CLINICAL RESEARCH NETWORKS: WHAT THEY DO AND HOW THEY HELP PAEDIATRIC RESEARCH**

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**ABSTRACT**

This review provides paediatricians with an update on the new structure of the National Institute for Health Research’s (NIHR) Clinical Research Network (CRN): Children and its role within the wider NIHR infrastructure.

The Network supports delivery of high quality research within the NHS in England and supports researchers, through provision of staff and resources, with feasibility, site set-up, patient recruitment and study management. Since 2013, over 80% of commercial contract studies running within the UK sat within the UKCRN Portfolio. Of the diverse, increasing Portfolio of studies supported by the Network, many studies are interventional, with 33% being randomized-controlled studies. Recruitment to studies supported by the Network through the Children’s Portfolio has consistently improved. Over 200,000 participants have been recruited to the Children’s Portfolio studies to date and there are currently approximately 500 studies open to recruitment. The CRN: Children has successfully involved patients and the public in all aspects of study design and delivery, including through the work of Generation R.

Challenges remain in conducting paediatric research and the Network is committed to supporting Children’s research and further building on its achievements to date. Education and engagement of paediatricians within the Network and research is important to further improving quality and delivery of paediatric research.

**AIMS OF REVIEW**

This article offers paediatricians an update on the new structure of the National Institute for Health Research’s (NIHR) Clinical Research Network (CRN): Children and its role within the wider NIHR. We consider specifically how the NIHR CRN has improved delivery of high quality child health research across the NHS in England and collaboratively as part of international studies.

**THE NATIONAL INSTITUTE OF HEALTH RESEARCH**

The CRN is an important part of the NIHR. The NIHR – ‘the research arm of the NHS’ - is funded by the Department of Health (DoH) for England to improve the health of the nation through clinical research. It was established in 2006 to help facilitate research to reach its full potential in the health system.[1]

There are four main work strands in the NIHR with patients and public at its heart, which is particularly important for considering the needs of children and young people. Research infrastructure is one of the work strands and includes a range of facilities such as Clinical Research Facilities (CRFs) and Biomedical Research Centres, working collaboratively with, and alongside the CRN.

**INTRODUCTION: THE CRN**

**Aims of the CRN**

The CRN (<https://www.crn.nihr.ac.uk>) supports high quality research within the NHS in England (see Table 1).[2] Trained research staff advise and support on aspects of study design and delivery including feasibility, site set-up, patient recruitment and study management. The CRN is focused in England and works closely and collaboratively with the corresponding Networks across the rest of the UK: Health and Care Research Wales ([www.healthandcareresearch.gov.wales/](http://www.healthandcareresearch.gov.wales/)); NHS Research Scotland ([www.nhsresearchscotland.org.uk/](http://www.nhsresearchscotland.org.uk/)); Northern Ireland Clinical Research Network ([www.nicrn.hscni.net](http://www.nicrn.hscni.net)). The systems in these Networks vary from those within the CRN in England but many processes are shared to aide researchers and provide consistency across the UK.

*Table 1: CRN aims [2]*

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| CRN Aims |
| * Promote equality of access, ensuring that wherever possible, patients have parity of opportunity to participate in research
* Improve the quality, speed and co-ordination of clinical research by removing the barriers to research in the NHS
* Streamline and performance manage NHS Support for eligible studies to ensure that the NHS Service Support Costs of these studies are met in a timely and efficient manner
* Work in partnership to unify and streamline administrative procedures associated with regulation, governance, reporting, and approvals
* Meet the research delivery needs of the life sciences industry including; pharmaceutical; biotechnology; diagnostic; medical technology; and contract research organisations (CROs)
* Further integrate health research and patient care
* Engage the NHS in research in line with the NHS Constitution to promote research participation and a research culture
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**New structure of the CRN**

The new CRN structure (from April 2015) includes fifteen Local Clinical Research Networks (LCRNs) across England along with a single National Co-ordinating Centre. The core aims of the LCRNs are to support recruitment of participants into eligible studies and ensure all studies are conducted to the highest standard. They promote research within their region and aim to increase involvement of district hospitals and other healthcare settings.

Each LCRN has a host NHS Trust / hospital that has a contract with the DoH to deliver the CRN Portfolio across the corresponding geographical area. Funding is provided to support delivery of studies in an effective and efficient manner. The LCRNs work closely with NIHR CRFs for Experimental Medicine, and other NIHR infrastructure, to support early phase and high-intensity studies. This includes approximately twenty UK-wide CRFs, which support paediatric studies (http://www.ukcrfnetwork.co.uk).

Paediatrics is one of thirty specialties supported by the CRN. There is a National Specialty Lead for each of the specialties including Children. Within each LCRN, a Local Children’s Lead has been identified to work with the local paediatric community to support delivery of the study Portfolio. These local leads work with the LCRNs and are responsible for maintaining a regional overview of Portfolio studies in their specialty, and facilitating delivery of Portfolio studies within local sites. The National Children’s Specialty group, chaired by the National Specialty Lead, brings the fifteen local leads together on a regular basis and is responsible for linking the CRN with external specialty-specific stakeholders such as charity funders and the life sciences industry and supporting collaboration of their specialty with other parts of the CRN.

**CRN Portfolio**

The NIHR CRN Portfolio is part of the UK Clinical Research Network (UKCRN) Portfolio, which consists of the Network Portfolios for England, Northern Ireland, Scotland and Wales. All UKCRN Portfolio studies are held on the UKCRN Portfolio database. The Portfolio contains high quality research studies that, within England, have access to CRN support.

The DoH have determined the eligibility criteria for Portfolio studies. All studies must be a “research study” (i.e. attempt to derive generalisable new knowledge by addressing clearly defined questions with systematic and rigorous methods) and have acquired funding prior to inclusion within the Portfolio. All non-commercial studies must have obtained funding through a nationally competitive, peer-reviewed process. Studies which have some of their research funded by the NIHR, other areas of central Government and NIHR non-commercial Partners are automatically eligible for inclusion on the Portfolio. Studies which are not automatically eligible must undergo a formal adoption process to be considered for inclusion. More details regarding eligibility criteria can be found at: https://www.crn.nihr.ac.uk/can-help/funders-academics/nihrcrn-portfolio/which-studies-are-eligible-for-clinical-research-network-support/. The researcher submits a Portfolio Adoption Form through the Integrated Research Application System (IRAS). Studies sponsored by the life sciences industry are also eligible for inclusion in the UKCRN Portfolio and are considered based on quality, relevance and feasibility. Commercial research is eligible for NHS service support and this is provided on a cost recovery basis.

Support is provided for eligible studies at sites, and may include support from CRN staff such as LCRN managers, research nurses, data managers, secretarial support and medical staff sessions. It may also include appropriate clinical service support such as pharmacy, radiology and pathology.

**CRN: CHILDREN**

CRN: Children supports therapeutic early and late phase clinical trials, pharmacokinetic, pharmacodynamic, pharmacovigilance and other high quality studies in all therapeutic areas except children’s oncology and child mental health, which are supported by CRN: Cancer and CRN: Mental health specialties respectively. A total of over 200,000 participants have been recruited to the Children’s Portfolio studies to date.[3] The SYCAMORE trial [4] provides a good example of the many ways in which the CRN: Children can support clinical trials (see Table 2).

*Table 2: Case Study – The SYCAMORE Trial [4]*

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| The SYCAMORE Trial: A randomised controlled trial (RCT) supported by CRN: Children with study design, set up and delivery |
| * Participants: Patients aged ≥2 to <18 years with persistently active juvenile idiopathic arthritis associated uveitis despite optimized methotrexate treatment.
* Intervention: Subcutaneous adalimumab every 2 weeks
* Comparator: Subcutaneous placebo injection every 2 weeks
* Outcome: Time to treatment failure
* Treatment of uveitis not responsive to methotrexate identified as a research priority by the Paediatric Rheumatology CSG
* Recruitment across multiple NHS sites involved 10 LCRNs as well as Scotland and Northern Ireland
* Patient and public involvement was proactively part of every part of the study prioritisation, design (including championing for use of a placebo), conduct, delivery overcoming hurdles and final implementation of the preliminary data
* CRN funded research nurses supported study set-up and delivered the study across multiple sites
* CRN national co-ordinating centre organised teleconferences between local Network managers to share successful recruitment strategies e.g. identifying sites with combined ophthalmology and rheumatology clinics had better recruitment
* LCRN manager facilitated meetings with local Sycamore team to review recruitment strategies and share successful strategies from other sites
* CRN national co-ordinating centre collated information on national recruitment
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**History of the CRN: Children**

Paediatric research was prioritised by the UK government for substantial investment as part of the strategy on Medicines for Children (2004). A key component of this was the establishment of the NIHR Medicines for Children Research Network (MCRN), part of the response to the introduction of the European Union (EU) Regulation on Medicinal Products for Pediatric Use which came into force in 2007. The EU Regulation included a requirement for all new licensing applications to include a Paediatric Investigation Plan to establish safety and efficacy in the paediatric age group, as well as adaptations for age-appropriate formulations; if the studies are completed the company can apply for a 6-month patent extension (regardless of whether a marketing authorisation is granted in the paediatric age group). For studies of safety and efficacy of older medicines in children companies can apply for a Paediatric Use Marketing Authorisation (PUMA) which will allow 10 years of data protection for use of that drug in children.[5]

The aim of the MCRN was to improve children’s health and alleviate suffering through the provision of better and safer medicines. The NIHR MCRN provided an organised network for the delivery of studies,[6] in addition to providing an infrastructure to support the development of new studies.

As part of the NIHR Comprehensive Clinical Research Network, the Paediatric (non-medicines) Specialty Group (PSG) was set up in 2009 and supported a national Portfolio of paediatric research studies that did not involve medicines.

Since April 2014, the NIHR CRN as a whole has undergone significant reorganisation to improve access for researchers, customers and patients and to streamline and simplify processes that support research delivery.[2] At this point the two Portfolios, of MCRN and PSG, came under combined management of the NIHR Clinical Research Network: Children’s Specialty to support delivery of all paediatric studies.[7]

**CRN: Children and industry**

The CRN: Children has developed a very successful working relationship with the life sciences industry, demonstrated by the growth of the commercial Portfolio below (see Figure 1). This partnership is important to ensure industry studies of the very latest new drugs and formulations are available to children and young people, and that the studies are feasible and applicable to clinical practice in the UK. There was an increasing need to engage with global pharmaceutical industry in order to influence programme and protocol development. In response to this the Children’s Research Industry Group (CRIG) was established in 2013 to improve the Network collaboration with industry; improve the support offered to industry; allow the Network to obtain advice on industry networks; provide a forum for discussion issues in paediatric research and to attract additional studies to the UK.[8] The membership of CRIG incorporates representation from large and small pharmaceutical companies, small and medium enterprises and contract research organisations who work together to inform network engagement with the pharmaceutical industry. Examples of how CRIG has worked to support CRN: Children include championing the need for appropriate formulations for children, and highlighting the benefits of incorporating the views of children and families in study design to the life sciences industry.

**Children’s Portfolio**

There are a wide range of studies in the Portfolio, all supported by the CRN: Children. At the time of writing (1st August 2016) there were 472 children’s studies open to recruitment or in set-up being supported by the CRN: Children. Since the CRN has been established approximately 1500 studies have been supported by the Children’s Specialty.

**Clinical Studies Groups**

Clinical Studies Groups (CSGs) work closely with the CRN and therefore will be described as part of this review. CSGs are multi-disciplinary, sub-specialty based multidisciplinary expert groups including patient/parent representatives which provide unique, joined-up access to paediatric academic and clinical expertise. CSGs are not directly funded by the DoH. Many of the fourteen CSGs linked to CRN: Children are in receipt of funding from relevant UK medical charities.[9] There are many UK wide strategies to continue to foster close collaborative working with a number of charities that support and fund paediatric research.

The CSGs work in both a reactive and proactive manner. They work reactively providing free of charge, expert advice to help researchers and the pharmaceutical industry develop high quality research proposals. They also work proactively through identifying priority areas for future research and supporting development of appropriate proposals. CSGs are designed to be the first contact for investigators with a research question in order to ensure the Network is able to have early input into the development of proposals to ensure feasibility and development of appropriate protocols.

CSGs include active researchers (clinical and other professionals such as nurses, pharmacists and physiotherapists), parents, charity representatives and paediatric drug formulation experts.

**Patient and Public Involvement and Engagement (PPIE)**

The active involvement and engagement of patients and the public in the deliverability of research, is at the centre of CRN activities. CRN: Children has been at the forefront of PPIE in research design and delivery for some time, especially in regards to the involvement and engagement of children and families. In 2006, the MCRN started its first Young Persons’ Advisory Group (YPAG) based at the Network’s co-ordinating centre in Liverpool. Since then the group has expanded nationally and been renamed as GenerationR (R for research), and includes five more groups in London, Nottingham, Birmingham and Bristol. Each group consists of approximately 10-15 young people aged 8-19 years of age and membership is open to any young person who has a chronic condition, experience of taking part in health research or a general interest in science or medicine.

The initial remit of GenerationR was to engage young people with research and to work in partnership with, and offer support to, researchers working on CRN Portfolio studies and across the wider NIHR. The group provides a forum for young people to learn about and comment on aspects of the research cycle from the identification of research questions to the dissemination of research findings. The group also works alongside national and European governing bodies, such as the National Research Ethics Service (NRES) and the European Medicines Agency (EMA) as well as organisations such as the Royal College of Paediatrics and Child Health (RCPCH) to help facilitate the design and delivery of ethically robust research for children.

With the paediatric research community increasingly focusing on the real-world relevance of research, the influence of GenerationR is growing dramatically. This shift in culture is further evidenced by the number of researchers approaching the group for support. An external evaluation undertaken by the National Children’s Bureau in 2013-2014, highlighted that the group were involved in over sixty activities to support individual research projects, of which ten included working with pharmaceutical companies.[10] Group activities however, tended to focus on the more practical elements of projects, such as the design of patient information sheets, assent/consent documentation, questionnaires, and interview schedules. Involvement in more strategic issues, such as the outcomes to be measured in the study, is less common but we are increasingly trying to engage researchers at the earliest stage possible in protocol development to ensure the outcomes and acceptability of the study to suit the needs of patients and families.

Due to the success of Generation R the concept of YPAGs has grown and several recent developments have taken place including:

* Establishment of a Global consortium of YPAGs known as International Children’s Advisory Network (iCAN) set up to provide a voice for children and families in peadiatric medicine through synergy, communication and collaboration
* Establishment of a GenerationR Alliance set up to bring together organisations with an interest in promoting the active involvement of children, young people and families in health research. The Alliance is responsible for developing an engagement strategy to support the involvement of children and young people in health research, provide national oversight, and promote collaboration across the NIHR and wider.
* Discussions with the European Medicines Agency and colleagues across Europe to set up a European YPAG Network (eYPAGnet) that will involve partnering with regulators, pharmaceutical companies, academia and patient organisations to influence the children’s research agenda.

**International context**

Collaboration of research networks across Europe and worldwide is important as there are often small numbers of children eligible for studies in individual countries. The EU Paediatric Regulation required the European Medicines Agency to develop a European network of national and disease-specific networks. The European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) was established in response to this.[11] The CRN: Children, and in its previous form as the MCRN, has been involved since its inception. The aim of the European network is to co-ordinate studies, develop the necessary scientific and administrative competencies and avoid unnecessary duplication of studies in children and young people. The Enpr-EMA facilitates productive collaborations between pharmaceutical companies, regulators and paediatric academia in Europe and globally.

**GROWTH OF THE NIHR CRN: CHILDREN’S PORTFOLIO**

The growth of the CRN in supporting children’s research is demonstrated through the rapidly increasing number of Portfolio studies. Since 2013, over 80% of commercial contract studies (phase II-IV, all specialties) running within the UK sat within the UKCRN Portfolio and a similar picture exists for non-commercial studies[12].

**Portfolio studies**

Since the establishment of the MCRN in 2005 and the Paediatric Specialty Group in 2009 there has been a diverse, increasing Portfolio of studies supported by the Network (see Figure 1). Many studies are interventional, with 33% being RCTs.[3] Figure 1 also demonstrates how the commercial study Portfolio has rapidly grown.

*Figure 1: Number of commercial and non-commercial studies entering Portfolio.*

*Note: These data have been used with permission from the NIHR CRN Co-ordinating Centre (CC).*

**Recruitment**

The Network has provided comprehensive support in recruiting participants for Portfolio studies. The new structure as CRN: Children continues to provide and seeks to further improve recruitment support. The number of participants recruited annually to children’s Network studies has increased ten-fold between 2006 and 2015. The Network has facilitated recruitment of over 200,000 participants to studies supported by MCRN, PSG and CRN: Children over the last ten years. Network support has supported recruitment to time and target of approximately 80% of studies since 2013.

**CHALLENGES SPECIFIC TO PAEDIATRIC RESEARCH**

While much has been done successfully to promote and streamline children’s research with the support of the CRN as highlighted in the recruitment figures, challenges remain in conducting children’s studies.

The burden of disease in children is usually disproportionately small compared to adults, diagnostic criteria may be less well defined and clinical outcomes may not be developed in a suitable form for use with children. The CRN: Children, particularly through working with CSGs, provides the infrastructure to enable organisations working together to focus and overcome these challenges. Further improvement and development of international collaborations remains important.

However, the most difficult challenge, key to the success of clinical studies, lies in recruitment of participants. Engagement of clinicians is essential to improving participation in research studies. A study evaluating attitudes of paediatricians towards randomised controlled trials found that clinicians with previous research experience were most knowledgeable and perceived most benefits from trial participation[13]. Indeed, a recent paper examined barriers for parents and practitioners in recruiting to paediatric clinical trials, concluding that while practitioners felt approaching families about research overburdened them, this feeling was not reciprocated by families[14].

While there are numerous research initiatives aimed at paediaticians such as RCPCH’s Turning the Tide[15], a recent survey of UK junior paediatric trainees (Specialist Trainee Levels 1–3) exploring their research experience found that 89% considered themselves to have had minimal or no clinical research experience during paediatric training[16]. Trainees considered research experience an important part of training but found opportunities limited (see Figure 2). Sixty-nine percent of trainees didn’t know who to ask for advice and support. Reported barriers included research opportunities being aimed at more senior trainees (therefore excluding junior trainees); an emphasis on service provision; opportunities relying on “word of mouth”; and inflexible training structures making taking time out for research challenging.

Figure 2: Survey results - trainees responding as ‘definitely’ or ‘probably’ to the questions described [16]

This survey highlights the challenges in developing paediatricians with a strong research knowledge base which will aid future recruitment and development of new clinical trials.

**GETTING INVOLVED**

Awareness and participation in research amongst paediatricians is crucial to enable the continued development of children’s studies, both within the UK and internationally. There are many opportunities for paediatricians, whether in training or at consultant level, to become involved in research, and a variety of routes through which this could be achieved. At the local level, each individual study requires an enthusiastic team to deliver it successfully; interested paediatricians can speak to principal investigators to find out how they may become involved, for example, through undertaking study specific training and joining the delegation log. In addition, for paediatricians wanting greater involvement or to develop research ideas, there are local forums to bring up these ideas and find out how to proceed, and we would encourage anyone with an interest to approach colleagues who are already involved in research, or their local LCRN children’s lead ([www.crn.nihr.ac.uk/networks/](http://www.crn.nihr.ac.uk/networks/)). Formal training is available as standalone clinical research fellow posts at some early phase Clinical Research Facilities.

**CONCLUSION**

The CRN is part of the NIHR and helps deliver high quality research within the NHS and disseminates best practice nationally. The Network has rapidly expanded its number of children’s studies and steadily improved recruitment to time and target. Education and engagement of paediatricians in research is important to further improving quality and delivery of paediatric research.

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