CLINICAL INVESTIGATION

Developing a national network for clinical research: the NIHR Medicines for Children Research Network

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From its formation in 2005 until the present day, the National Institute for Health Research (NIHR) Medicines for Children Research Network (MCRN), in England, has recruited 25,000 children into over 300 trials. This has been achieved by the formation of a research network infrastructure embedded into the existing NHS led by a national Co-ordinating Center. Through the creation of subspecialty academic groups an extensive yet balanced portfolio has developed, including high-quality clinical trials and other well-designed studies funded by both public-funding bodies and the pharmaceutical industry. This review will describe the vision, mission and objectives of the MCRN from innovation to current structure and will outline its function, achievements and the path it is taking to achieve the vision to improve children's health and alleviate suffering through the provision of better and safer medicines.

Keywords: consumer involvement • Medicines for Children Research Network • pediatric drug trials • recruitment • research network

Gemma L Saint[1], Vanessa Poustie[2] & Rosalind L Smyth*[3]

[1]University of Liverpool, Institute of Child Health, Alder Hey Children's Hospital, Liverpool, UK
[2]NIHR Medicines for Children Research Network, Institute of Translational Medicine (Child Health), Alder Hey Hospital, Liverpool, UK
[3]Liverpool Health Partners, University of Liverpool, 2nd Floor, Foundation Building, 765 Brownlow Hill, Liverpool, L69 7ZX, UK
*Author for correspondence:
Email: r.l.smyth@liv.ac.uk

Clinicians should base decisions about treatments for their patients on the best available evidence about their effectiveness and safety. For pediatricians that has been challenging because of inadequate or no evidence about the use of medicines in the pediatric age group [1]. The practice of prescribing unlicensed or off-label drugs in children is widespread. On in-patient wards, in the UK, 25% of prescriptions used for children fall into this category [2] and in some parts of Europe this figure rises to 46% [3]. The problem is greatest in the neonatal population where 90% of patients receive a drug that is either unlicensed or used in an off-label way [4]. Children cannot be treated as 'small adults' with doses extrapolated from adult data. Profound differences in absorption, metabolism, distribution and excretion of substances can lead to undesired consequences such as passage through the blood–brain barrier or toxicity [5].

In 2007 the EU Regulation on Medicines for Pediatric Use became law in every European member state [6]. The purpose of the legislation is to increase the quantity and quality of research carried out on medication for pediatric use, improve the availability of adapted formulations and add to the amount of licensed medications. This is being achieved through incentives and requirements of pharmaceutical companies seeking a marketing authorization for a product in any patient group in Europe. All new licensing applications need to include a Pediatric Investigation Plan detailing a strategy for all studies required to establish safety and efficacy in the pediatric population, including adaptations needed to provide age-appropriate formulations. The only exclusions are for products that will not have any indication in the pediatric population. If the proposed studies are completed, regardless of whether a marketing authorization is granted in the pediatric population, the company can apply for a 6-month patent extension

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on the active moiety. For older medicines, if new studies are carried out providing evidence on safety or efficacy in children, then the company can apply for a Pediatric Use Marketing Authorization, which will allow 10 years of data protection for the use of that drug in children.

In 2004, while this Regulation was being developed, in the UK, the Medicines and Healthcare Regulatory Agency and Department of Health developed a Pediatric Strategy, which included measures to make better information about medicines for use in children to prescribers and the public [101]. They stated the objective of establishing a national network within the UK's NHS to support the conduct of studies that assessed the efficacy and safety of medicines in children. The NIHR MCRN is part of the NIHR Clinical Research Network (CRN), which provides a comprehensive infrastructure within the NHS to support research.

In 2004, the vision was laid out that the MCRN would be "*a network which will provide leadership and a world class environment to conduct clinical trials throughout the whole range of healthcare. We intend that in 5–10 years time, this network will be internationally recognized as the best of its kind worldwide. This will provide significant benefit for children through the new knowledge gained by excellent research and the subsequent improvements in care. Our network will be attractive as a resource for biotechnology and pharmaceutical companies internationally and will make the UK uniquely attractive, so that industrial development and wealth generation can be added to the primary focus on benefits for children*" [7]. This article will outline the launch of the MCRN, its successes to date and its future vision.

Development of NIHR MCRN infrastructure

In 2005 a consortium, led by the University of Liverpool, competitively gained the contract for a Coordinating Center that would establish and lead the MCRN (MCRNCC). The consortium, which comprized the University of Liverpool (Liverpool, UK), Alder Hey Children's NHS Foundation Trust (Liverpool, UK), Liverpool Women's NHS Foundation Hospital (Liverpool, UK), Imperial College London (London, UK), National Children's Bureau (London, UK) and National Perinatal Epidemiology Unit, University of Oxford (Oxford, UK), became the MCRN Executive Committee. MCRNCC commenced work first by appointing core staff and then by setting up local research networks (LRNs) and establishing key research objectives. Over time, the role of the Coordinating Center has evolved from establishment of the network to performance management and the delivery of the portfolio of studies. It maintains an overview of all the LRNs, which it meets twice a year for performance meetings to review portfolio and contribution to the MCRN.

The initial strategic focus was to develop the MCRN portfolio and the MCRNCC first established sub-speciality based Clinical Studies Groups (CSGs), which are multidisciplinary academic groups with expertise to advise on the design of studies within their clinical area. There are now 15 MCRN CSGs and many are additionally funded by relevant UK medical charities (Box 1). The CSGs are the driving force behind the MCRN portfolio. Their role is both proactive and reactive. First, they provide expertise in particular subject areas to support investigators and industry in the planning and establishment of new studies, and second, they identify priority areas for research and lead on the development of appropriate proposals. They are designed to be the first point of contact for investigators with a research question; in this way the network is able to have early input in the development of proposals to ensure feasibility and protocol appropriateness. The Methodology and Pharmacology CSGs also participate at this stage on study design as appropriate.

The MCRNCC then established an infrastructure across England to support recruitment into clinical studies. Following a competitive appointment process, a structure of six LRNs were established, between them covering around half of the geographical area of England. The core activities of the LRNs are to support recruitment of participants into eligible studies, and ensure that studies are conducted to the highest standards of clinical governance. They are tasked with promoting research in their region, including increasing the involvement of district hospitals. Each LRN is led by a management team overseen by an advisory board consisting of both clinicians and academics involved in every aspect of pediatric care. This infrastructure has subsequently been expanded to cover all of England, in partnership with comprehensive LRNs. Funding has been provided to each LRN in order that the foundations are in place to support the conduct of multicenter trials in an effective and timely manner.

The robust infrastructure of the MCRN described above is what underpins the subsequent success of studies. However, the procedure of ensuring that portfolio studies are feasible and appropriate is also of fundamental importance. All studies have secured funding prior to inclusion/adoption on the portfolio. All noncommercial studies have obtained funding through a nationally competitive, peer-reviewed process, often from NIHR funding programmes. The MCRN Study Assessment Committee (SAC) have the task of considering both commercial and publicly funded studies for inclusion onto the MCRN portfolio. The committee has a wide membership comprising of physicians, nurses, pharmacist and parents. Studies that are eligible for automatic inclusion are discussed in relation to feasibility and how the network can best support recruitment of children to time and target. Consideration of industry studies for portfolio enrolment is based on quality, relevance and feasibility. The close working of the SAC and CSGs is essential to ensure a balance within the portfolio.

Box 1. Clinical Studies Groups (collaborative funding bodies).

- Allergy, Infection and Immunity (MCRN/BPAIIG collaboration)
- Anesthesia, Pain, Intensive Care and Cardiology
- Cleft and Craniofacial Anomalies (MCRN/Healing Foundation and Craniofacial Society of Great Britain collaboration)
- Diabetes and Endocrine (MCRN/BSPED collaboration)
- General Pediatrics (MCRN/BAGP collaboration)
- Inherited Metabolic Disorders (MCRN/UK Lysosomal Storage Disorders Patient Collaborative Group collaboration)
- Methodology
- Neonatal (MCRN/Action Medical Research collaboration)
- Neurosciences
- Pain and Palliative Care (MCRN/Louis Dundas Development Fund collaboration)
- Pediatric Gastroenterology, Hepatology and Nutrition (MCRN/BSPGHAN collaboration)
- Pediatric Nephrology (MCRN/BAPN collaboration)
- Pediatric Rheumatology (MCRN/Arthritis Research UK collaboration)
- Pharmacy and Pharmacology
- Respiratory and Cystic Fibrosis (MCRN/BPRS collaboration)

BAGP: British Association of General Paediatrics; BAPN: British Association for Paediatric Nephrology; BPAIIG: British Paediatric Allergy Immunology and Infection Group; BPRS: British Paediatric Respiratory Society; BSPED: British Society for Paediatric Endocrinology and Diabetes; BSPGHAN: British Society for Paediatric Gastroenterology Hepatology And Nutrition; MCRN: Medicines for Children Research Network.

MCRN workstreams

The involvement of a clinical trials unit (CTU) is encouraged for investigators carrying out clinical trials through the network. The MCRN CTU was established in order to conduct and provide support for MCRN-supported clinical trials. It is the first UK CTU, outside oncology and neonatology, to be dedicated to the conduct of clinical trials for children and provides expertise in statistics, trial management and data management relevant to clinical trials. Extensive assistance is available in every aspect of study design and management including grant applications, protocol development, regulatory authority and research ethics committee submissions, data management and analysis and the preparation of reports for data monitoring committees. Standard operating procedures have been developed around all of these issues.

Involvement of children, young people and families is integral to the work carried out in all aspects of the MCRN; their views are central to all elements of the research process. Their participation has been ensured through the formation of a Consumer Involvement Steering Group (CISG) who engage with all activities performed by the MCRN. On each CSG sit parent/carer representatives who have valuable input identifying priority areas for research. Parent/carer representatives also sit on the SAC. One of the first established consumer initiatives was the Young Persons Advisory Group, set up in 2006 in Liverpool. Their contribution includes advising on study design and acceptability, reviewing age-appropriate patient information, participating in science fairs and presentations about their work at relevant conferences. There are now groups based in the East, the West Midlands, the South West and London who form one National Advisory Group.

Review of performance of MCRN

As of March 2012, the portfolio had 327 studies; 157 open to recruitment or in set-up. Of these studies, 52% were sponsored by the pharmaceutical industry. The majority of the studies are randomized control trials, of which two-thirds were late-phase trials. Most trials were multicenter and most noncommercial studies were coordinated by, or associated with, a CTU. An important minority of studies are qualitative in design, the object of which is to assist in our understanding of the process and impact of pediatric medicines research, focusing on study design and research acceptability to patients and families.

It is not just the number or rapid increase in trials and other well-designed studies (Figure 1), but the quality and subsequent results with direct impact on clinical practice that shows the extent of the MCRN's accomplishment. There have been a number of very large trials that prior to the MCRN's facilitation would have been untenable. The MAGNETIC (HTA-funded) study is one such example, detailed in Box 2, with 508 children randomized in 33 acute emergency department sites and closing to time and target. The MCRN-supported study of the Prevenar 13 vaccine has led to its license across the world and it is now part of the routine vaccination schedule for all children in England [8]. The drug tocilizumab has been NICE-approved following an industry-funded placebo controlled study in children with systemic juvenile

Box 2. Case study 1: MAGNETIC trial.

- Participants: children aged 2–16 years presenting to hospital emergency departments/acute inpatient units with severe acute asthma
- Intervention: nebulized magnesium as an adjunct to nebulized salbutamol and ipratopium bromide on three occasions at 20 min intervals
- Comparator: nebulized saline as the adjunct
- Outcome: clinical improvement, additional treatment, length of stay
- Phase III interventional, single randomization, target: 507
- Impact: despite the challenging accident and emergency setting, there was successful recruitment at hospitals that were unfamiliar with clinical trials in acute settings. New sites and staff were introduced to clinical research

Box 3. Case study 2: Tocilizumab trial.

- Participants: children aged 2–17 years with systemic juvenile idiopathic arthritis with persistent activity and inadequate response to NSAIDs and systemic corticosteroids
- Intervention: intravenous tocilizumab administered fortnightly for 12 weeks
- Comparator: intravenous placebo administered fortnightly for 12 weeks
- Outcomes: reduction in symptoms by at least 30%
- 12-week randomized, double-blind, placebo-controlled, two-arm study
- Global target: 108; UK target: seven
- UK exceeded target, recruiting eight patients. Tocilizumab has now received NICE approval and children as young as 2 years of age are benefiting from this new treatment

idiopathic arthritis, outlined in Box 3.

The Requirements of Industry laid out in the European Regulation have been a catalyst for the increase in industry-funded pediatric drug trials (Figure 1). The MCRN Industry Team has responded by building extensive contacts with pharmaceutical companies, providing guidance and expertise, and ensuring the availability of an efficient clinical studies infrastructure. By focusing on performance, meeting recruitment targets and delivering to time, the UK has been promoted as an efficient location for clinical research. Because of the support from MCRN infrastructure, recruitment of children to clinical studies has increased within England, as well as ensuring the robustness and relevance of outcomes for this patient population. In order that studies are feasible to be conducted in the UK, MCRN, through its CSGs, is aiming to have input in the development of commercial protocols. Following the development of the protocol, significant resources are employed to carry out feasibility assessments in order to ensure that subsequent study targets will be attainable. This approach and the MCRN's success in conducting industry-sponsored studies and the increase in proportion of these studies in the portfolio looks set to continue as more Pediatric Investigation Plans are approved.

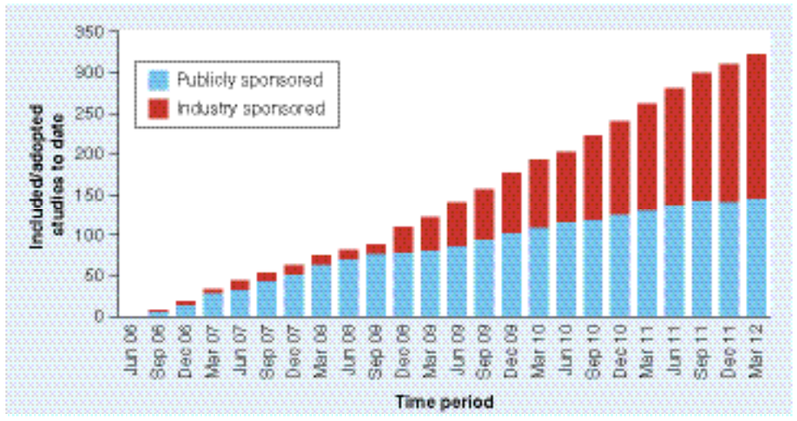

Figure 1. Growth of the Medicines for Children Research Network portfolio. The steady increase of Medicines for Children Research Network studies from June 2006 to March 2012. The split of industry to publicly sponsored studies is shown, with just over half of all studies now being industry sponsored.
Reproduced with permission from [10].

Future perspective

Approximately 25,000 children have been recruited to MCRN Portfolio studies to date (Figure 2). Recruitment in 2009/2010 was boosted by the participation of 993 children in an H1N1 vaccine trial [9] and these figures were matched the following year. The focus within the MCRN is shifting towards performance management, specifically in the areas of meeting recruitment targets. In 2008, 32% of studies had recruited more than 80% of their current target and this has increased; by the end of 2010 this had risen to 64% for the 50 closed studies. The aim is to continue this increase and see it rise to 80%. The growth in the MCRN study portfolio indicates a renewed interest, acceptance and enthusiasm for pediatric research in England, amongst physicians, industry, patients and families. The MCRN are now focusing on supporting more pediatricians and centers in order that a larger number of children can have access to these studies.

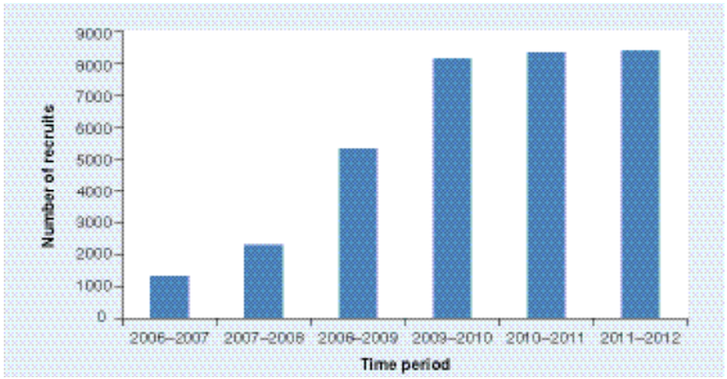

Figure 2. Medicines for Children Research Network recruitment. The number of recruits in England into Medicines for Children Research Network studies per year from 2006–2007 to 2011–2012.
Reproduced with permission from [11].

Executive summary

- The National Institute for Health Research Medicines for Children Research Network's (MCRN) vision is to improve children's health and alleviate suffering through the provision of better and safer medicines.
- The MCRN is a large network that supports studies of medicines for children in NHS sites serving around 12 million children.
- In total, 25,000 children have been recruited to over 300 MCRN portfolio studies.
- Benefit is seen for children at point-of-care, for example, by the evolution of a new NICE-approved medicine and superior vaccines on the national schedule.
- The MCRN plan to continue to engage clinicians and promote research across England, maintaining and improving upon the high level of performance seen since conception.

Disclaimer

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