The need to evaluate medicines for children is widely acknowledged due to pervasive unlicensed medicine use in the pediatric setting. The EU Paediatric Regulation was developed to address these considerations, which subsequently led to the establishment of the National Institute of Health Research (NIHR) Medicines for Children Research Network (MCRN) in England. MCRN supports public and industry studies, and facilitates feasibility, site setup, recruitment and other services. The MCRN and other networks are members of the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA). Enpr-EMA was established to foster and coordinate research, and develop collaborations across Europe. MCRN works with Enpr-EMA, industry and others to improve the conduct of research for the benefit of children’s health.

Economic, ethical and other considerations associated with the conduct of pediatric research have limited the numbers of clinical trials conducted with children [1]. Due in part to the lack of evidence of efficacy and safety of medicines in the pediatric setting, there has been widespread unlicensed and off-label medicines use in this vulnerable population [2,3]. This lack of relevant information can potentially lead in turn to undesired consequences such as under and overdosing, and adverse events [4,5], as well as impacting negatively on clinical outcomes [101,102]. Therefore, there is widespread acknowledgment of the need for further evaluation of medicines for children in well-designed studies, including development of age-appropriate formulations.

The above considerations led to the US and EU legislation to improve the availability of information on the use of medicines for children and provide incentives for companies to carry out pediatric clinical trials. The EU Paediatric Regulation came into force in January 2007 [6,7,103] and requires companies to produce a 'Paediatric Investigation Plan' (PIP) for all new medicinal products, detailing the clinical studies to be undertaken with children. PIPs are also required when the use of patented products is being extended to a new indication or for off-patent medicines to be developed specifically for children. PIPs have to be agreed with the EMA’s Paediatric Committee (PDCO) prior to the submission of a marketing authorization. All pediatric studies must be completed in compliance with the approved PIP in order for the medicine to be eligible for 6 months’ supplementary protection certificate (SPC) extension. In the case of an off-patent medicine developed specifically for children and with an age-appropriate formulation, the sponsor can benefit from a Paediatric Use Marketing Authorisation (PUMA) with a 10-year period of data/market protection.

In response to the EU Paediatric Regulation and in recognition that more needed to be done to address the widespread unlicensed and off-label medicine use in children, a number of national pediatric research networks have been established. In England, the National...
Table 1. MCRN Clinical Studies Groups, with charity supporters and professional body affiliations shown.

<table>
<thead>
<tr>
<th>Clinical Studies Group</th>
<th>Charity Supporter/Professional Body Affiliation</th>
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<tbody>
<tr>
<td>Allergy, Infectious Diseases and Immunity (MCRN/BrPaediatric Allergy Immunology and Infection Group collaboration)</td>
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<tr>
<td>Anaesthesia, Pain, Intensive Care and Cardiology</td>
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<tr>
<td>Cleft and Craniofacial Anomalies (MCRN/Healing Foundation/ Craniofacial Society of Great Britain and Ireland collaboration)</td>
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<tr>
<td>Diabetes and Endocrine (MCRN/BrPaediatric Endocrinology and Diabetes collaboration)</td>
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<tr>
<td>Gastroenterology, Hepatology and Nutrition (MCRN/BrPaediatric Gastroenterology, Hepatology and Nutrition collaboration)</td>
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<tr>
<td>General Paediatric</td>
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<tr>
<td>Inherited Metabolic Disorders (MCRN/UK Lysosomal Storage Disorders Patient Collaborative Group collaboration)</td>
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<td>Methodology</td>
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<td>Neonatal (MCRN/Action Medical Research collaboration)</td>
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<td>Nephrology</td>
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<td>Neurosciences</td>
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<tr>
<td>Pain and Palliative Care (MCRN/Louis Dundas Development Fund collaboration)</td>
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<tr>
<td>Pharmacy and Pharmacology</td>
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<tr>
<td>Respiratory and Cystic Fibrosis</td>
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<tr>
<td>Rheumatology (MCRN/Arthritis Research UK collaboration)</td>
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<tr>
<td>MCRN: Medicines for Children Research Network.</td>
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Institute for Health Research (NIHR) Medicines for Children Research Network (MCRN) was established in 2005 to improve children’s health and alleviate suffering through the provision of better and safer medicines. MCRN with other specialist and comprehensive networks is part of the NIHR Clinical Research Network (CRN), which supports research to make patients, and the National Health Service (NHS) in England, better. The MCRN has a specific remit to improve the ability of the NHS to conduct children’s studies. Since the MCRN’s establishment, the network has worked to proactively support the setup, delivery and conduct of children’s studies and is now supporting close to 450 industry and public (non-commercial) studies. To illustrate the roles and remit of key elements that comprise a national children’s clinical research network, this article highlights i) how MCRN supports both industry and public studies, ii) the coordinating ‘European Network of Paediatric Research at the European Medicines Agency’ (Enpr-EMA) and iii) future areas of development for MCRN and others interested in pediatric research, with a focus on working more closely with industry through the newly formed Children’s Research Industry Group (CRIG).

**MCRN support for children’s research**

The MCRN supports publicly and industry-sponsored studies in NHS sites in England, and links in with research networks in Northern Ireland, Scotland and Wales. The network supports therapeutic clinical trials and pharmacokinetic, pharmacodynamic, pharmacovigilance and other studies, in all therapeutic areas except children’s oncology, which is supported by the NIHR Cancer Research Network. The MCRN Coordinating Centre is hosted by the University of Liverpool at the Alder Hey Children’s NHS Foundation Trust, and manages the activities of the groups outlined below. The network supports investigators and companies at all points in the development of a study, from an initial idea through to PIP and protocol development, assisting with feasibility, site setup, patient recruitment and study delivery.

**EU Paediatric regulation, protocol & other advice**

Companies and investigators can approach the MCRN for support with program and protocol development. Advice on program and protocol development is provided by the MCRN’s advisory Clinical Study Groups (CSGs), which cover the majority of pediatric specialities (Table 1). CSGs are multidisciplinary and include doctors, nurses, pharmacists, basic scientists, methodologists and parent/carer representatives. In addition to their advisory role, CSGs identify research priorities and develop their own study proposals to address important research questions. Typically, CSG members are not paid for their involvement by MCRN, so demands made on their time have to be carefully considered. The MCRN advises on pharmacy and formulations matters during study development and delivery, and facilitates children/family input into research (as described in further detail below).

**Children & family input into research**

The MCRN advises on child/patient/parent/carer matters, operating very active Young Persons’ Advisory Groups. Engaging with young people as championed by MCRN is innovative and has led to improvements in the quality of patient information, the design of studies to improve their delivery and the changes to national guidance (Box 1). Children/young people apply to join groups and are selected on the basis of whether they have understood the group’s objectives, their motivations and on any relevant clinical experience (although this is not a requirement for membership). Young people are integral to making decisions on the activities that the groups undertake.

**Infrastructure**

Currently, six regional MCRN Local Research Networks (LRNs) and three Areas, covering England, assist investigators/sites working on studies in NHS sites. Over 120 pediatric research staff work in Local Research Networks to provide a range of support with feasibility, site setup, patient recruitment support and performance management, outlined in the sections below. MCRN staff work in close collaboration with NIHR Paediatric Clinical Research Facilities (CRFs) for
Experimental Medicine to support industry and public research. There are more than 16 children’s CRFs in the UK that support high-intensity studies, including pharmacokinetic and pharmacodynamic research.

NIHR CRN has been in operation for 7 years and, after careful review, is undergoing reorganization to improve access for research, to harmonize and simplify processes in order that the quality of research support and delivery can be further improved. The new system will be in operation during 2014 and for children’s research, providing enhanced national coverage and ability to support all appropriate children’s research [106].

Feasibility
The MCRN supports top-level, UK-wide assessments of study feasibility through the CSGs. The network also identifies investigators/sites that are interested in working on studies, with industry feasibility services recently being refined through a national, NIHR CRN-led service improvement program. Initial site identification is typically completed within a 15 working day period. Starting with feasibility, the MCRN Local

Box 1. MCRN Young Persons’ Advisory Groups.

The MCRN has been at the forefront of patient and public involvement in research since its establishment. In 2006, the network started its first Young Persons’ Advisory Group in Liverpool, UK. Establishing this group required significant effort, and since then, four more groups have been established in London, Nottingham, Birmingham and Bristol. The initial remit of these groups was to engage young people with research and to support researchers in the design and delivery of their studies, activities which have been very successful and helped to ensure that protocols and child/parent/carer information are relevant [8]. Subsequently, groups have started to collaborate with national governing bodies (e.g., the UK’s NRES), helping them to remodel the guidance for researchers on the design and delivery of ethically robust studies for children [104].

Young Persons’ Advisory Group members felt that NRES guidance was producing study materials that were formulaic, designed to tick legal and governmental boxes, too long and ultimately failed to meet the needs of children and young people. From discussions, NRES learnt that one of the guiding principles for producing information for young people is that they want to understand research and its impact on their lives. NRES will be incorporating the group’s feedback into their guidance to help researchers understand how to provide study materials for children (at the time of writing (May 2013), updated guidance will be shortly added to the NRES website [105]). Input from the Young Persons’ Advisory Group is not restricted to academic/NHS researchers: the number of life-sciences organizations now approaching the group for support has grown dramatically, with an average of one new company contacting the MCRN each month. In September 2013, the group is also holding its first national event in which a wider range of organizations will gain an insight into how young people and families have a positive impact on the development of clinical research.

Box 2. Magnesium Nebuliser Trial in Children (MAGNETIC).

The MAGNETIC study was funded by the NIHR Health Technology Assessment program and sponsored by Cardiff University [110,111]. The study took place at A&E departments and/or pediatric assessment units at 33 sites throughout the UK and analyzed the effect of supplementary magnesium nebulizers on the recovery of children experiencing severe asthma attacks. By early 2011, it had succeeded in meeting its recruitment target of 500 young people between the ages of 2 and 16 in just over 2 years. Significantly, it managed to do so without relying exclusively on established research centers. MCRN Local Research Networks and Areas supported sites, including many smaller hospitals with limited research experience, with assistance with research approvals, training and recruitment. MCRN research nurses were able to support many investigators/teams, helping them to achieve their recruitment targets by navigating clinical and procedural challenges. Obtaining informed consent was a particular challenge, with only 30 min to screen, consent and randomize patients. Continual training of new site staff was key to the study’s success and MCRN teams around the country were able to facilitate a comprehensive program of education and the sharing of best practice. MAGNETIC had a clear legacy beyond its important findings [9,112]. It introduced new sites to clinical research across the UK and gave more patients the opportunity to take part. It has also enabled staff to develop new skills and left many health professionals looking forward to their next research experience.

Research Network/Area staff ensure that clinical studies involving children are performed efficiently to the highest standards across NHS sites.

Site setup
Rapid site setup is critical to the success of a study. To support this, the MCRN assists with study setup following site and country selection. Network staff work with sites to assist with study costing, local ethics and R&D approvals, contracting and staff training. As well as improvements with ethical and NHS R&D approval processes, study costing has continued to be significantly assisted by the development of NIHR CRN costing templates [107], and for study contracting, the MCRN uses standard contracts (i.e., the model Clinical Trial Agreement [mCTA]) to expedite negotiations [108].

Patient recruitment/study delivery
MCRN staff work with NHS sites and sponsors to ensure that studies are conducted rapidly to a high standard. In particular, the network ensures that research nurse and other site support is appropriate and can provide assistance with patient recruitment and data collection. MCRN, as part of NIHR CRN, works within a performance management framework [109]. Central to this framework is the continual monitoring of recruitment to studies by local and Coordinating Centre staff, with additional support (such as research nurse support) provided to sites if necessary. Upon closure of the study, network staff
work with sites/sponsors to ensure that all regulatory and other requirements are addressed. The support that MCRN provides to companies and public investigators has led to exceptional study performance, with approximately 80% of studies recruiting to time and target (FIGURE 1) and approximately 30% of international multicenter studies recruiting their first participant in the UK. Studies that the MCRN has supported are now informing licensing decisions and clinical practice (e.g., tocilizumab (RoActemra) in systemic juvenile idiopathic arthritis (sJIA), the Menveo vaccine in meningococcal disease, Kalydeco (ivacaftor) in cystic fibrosis, Prevenar 13 vaccine in pneumococcal disease, Cozaar in proteinuria and Xalatan (Latanoprost) in glaucoma).

**Study portfolio metrics**

As of May 2013, the MCRN has adopted 246 commercial and 192 public studies into its portfolio. The portfolio covers all topics represented by CSGs (FIGURE 2). MCRN studies now recruit in excess of 10,000 participants on an annual basis (FIGURE 3). The MCRN’s industry study portfolio has grown rapidly and now represents 56% of all studies supported by the network (FIGURES 4 & 5). Given the number of industry studies that the MCRN has been approached to support and the licensing decisions to date (see recent examples above), it is clear that the EU Paediatric Regulation has led to a fundamental change in the approach that companies are taking to develop medicines and as a result more child-appropriate medicines will be developed.

**Working across Europe**

Given that there are often small numbers of children eligible for studies in individual countries, it is necessary to collaborate closely with networks in countries across Europe and beyond to ensure study delivery. Currently, industry and on occasion public sponsors coordinate activities across multiple countries. However, going forward, it will be necessary to promote greater collaboration between European networks. Under the EU Paediatric Regulation, the Enpr-EMA, a network of research networks, investigators and centers has been established to fulfill this need [10]. The details of networks involved with Enpr-EMA are provided on the EMA website [113], with disease-specific (e.g., Pediatric Rheumatology International Trials Organisation (PRINTO) and national networks (including MCRN) involved. The main objectives of Enpr-EMA are to:

- Foster high-quality, ethical research on the quality, safety and efficacy of medicines for use in children,
- Enable collaboration between networks and stakeholders,
- Coordinate studies relating to pediatric medicines and avoid unnecessary testing in children,
- Build up scientific and administrative competence at a European level,
- Help with the recruitment of patients for clinical trials, and
- Promote European Commission framework program applications.

Given Enpr-EMA’s objectives/activities, it has a range of stakeholders beyond constituent networks (including...
the pharmaceutical industry, Contract Research Organisations (CROs), patients/parents, patient organizations, National Competent Authorities, Ethics Committees), and interacts with them through an annual workshop and other meetings. MCRN works closely with Enpr-EMA and its constituent networks to share best practice, provide advice on studies/programs, identify research centers and collaborate on a range of other issues. It should be noted that the level of funding that MCRN receives from government sources is unique across Europe, and this has allowed MCRN to develop an effective infrastructure and for the UK to capitalize on the Paediatric Regulation. Colleagues in other parts of Europe consider that more funds should be made available from their governments or from central European budgets to develop their network capacity or a pan-European infrastructure [114].

Future initiatives

In addition to responding to requests to advise on/support studies, the MCRN supports initiatives to enhance the services that it offers, particularly in relation to the NIHR CRN performance management framework as referred to above. One major new initiative to improve i) collaboration with and ii) services offered to pharmaceutical companies, CROs and other companies is the establishment of MCRN of the CRIG. In the past, the MCRN’s liaison with industry representatives has not been formalized. However, with increasing numbers of industry studies supported by MCRN and partners there are continued efforts to improve our collaboration with industry. The CRIG has recently been established, linking MCRN and other organizations (including Children’s CRFs), with representatives in industry working on children’s medicines, devices and other areas. The group aim to improve collaboration with industry (in particular during early program development), improve the support that we offer industry, allow MCRN and other affiliated organizations to obtain advice on industry matters, provide a forum for the discussion of children’s research issues and to attract additional studies to the UK.

In early 2013, 15 senior industry professionals with children’s clinical research expertise were recruited to the group (primarily from pharmaceutical companies and CROs) following an open advert circulated via professional bodies, the MCRN website and through industry contacts. We received high quality applications from both the UK and international colleagues. Additional members with further experience of children’s devices, diagnostics, gene therapy and stem cell therapy will also be proactively sought, as limited applications from colleagues with expertise in these areas were received.

The first meeting of CRIG took place in May 2013 in London. The focus of the first meeting was to i) introduce group members to the clinical research infrastructure in England, ii) introduce them to the range of industry studies for children supported to date, iii) discuss the objectives of the group and iv) explore areas for future discussion/group activity. A number of key initial activities were identified. First, it was agreed that children’s networks need to work together (for instance, with Enpr-EMA) to publicize globally, the opportunities of working with the pharmaceutical industry to improve children’s trials. Equally important is constructive dialogue with regulators to ensure that their requirements can be matched in feasible pediatric studies [11]. It is hoped that these collaborations will facilitate innovative trial designs for children’s studies (e.g., Bayesian designs, extrapolation approaches and even methods to compare multiple investigational products in the same study). The group hope that there will be further developments to improve pharmacokinetic, formulations and dosing methodologies for children.

Figure 3. The total recruitment to Medicines for Children Research Network (MCRN) studies on an annual basis since MCRN was established.

Figure 4. The growth of the Medicines for Children Research Network study portfolio.
suggestion that the EU Paediatric Regulation has led to a fundamental change in the approach that companies are taking to developing medicines. Going forward, the MCRN within the wider NIHR CRN is to undergo reorganization to improve still further its effective and efficient support for children’s clinical studies. Working with Enpr-EMA and children’s research networks across the world allows MCRN to share best practice and collaborate on a range of other issues. Over the next 5 years, MCRN will collaborate with companies, regulators, Enpr-EMA and other networks and organizations to improve the design and delivery of children’s research studies/programs. This is likely to require activities including i) improved interaction between companies and networks at an earlier stage in the product development cycle, ii) collaboration with regulators/Enpr-EMA to improve the feasibility of studies and iii) the development of innovative study methodologies and improved formulations for children.

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No writing assistance was utilized in the production of this manuscript.

Key issues

- Economic, ethical and other considerations associated with the conduct of pediatric research have limited the numbers of clinical trials conducted with children. However, this has led to widespread unlicensed and off-label medicine use; there is widespread acknowledgment of the need for further evaluation of medicines for children in well-designed studies.
- The above considerations led to the US and EU legislation to improve the availability of information on the use of medicines for children and provide incentives for companies to carry out pediatric clinical trials. The EU Paediatric Regulation came into force in January 2007.
- In response to the EU Paediatric Regulation and in recognition that more is needed to be done to address the widespread unlicensed and off-label medicine use in children, a number of national pediatric research networks have been established.
- In England, the National Institute for Health Research (NIHR) Medicines for Children Research Network (MCRN) was established in 2005 to improve children’s health and alleviate suffering through the provision of better and safer medicines. Going forward, the MCRN within the wider NIHR CRN is to undergo reorganization to improve still further its effective and efficient support for children’s clinical studies. Working with Enpr-EMA and children’s research networks across the world allows MCRN to share best practice and collaborate on a range of other issues. Over the next 5 years, MCRN will collaborate with companies, regulators, Enpr-EMA and other networks and organizations to improve the design and delivery of children’s research studies/programs. This is likely to require activities including i) improved interaction between companies and networks at an earlier stage in the product development cycle, ii) collaboration with regulators/Enpr-EMA to improve the feasibility of studies and iii) the development of innovative study methodologies and improved formulations for children.

Figure 5. The rapid growth of the Medicines for Children Research Network industry study portfolio. Studies classified as early Phase (I and II), late Phase (III and IV) or cohort.
References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest


•• Key paper outlining ethical dilemmas associated with consent and recruitment.


•• Key reference for the Paediatric Regulation.


•• Reflections on the involvement of young people to improve research.


Websites


105 National Research Ethics Service website. www.nres.nhs.uk/

106 NIHR Clinical Research Network website: Evolving the network page. www.crncc.nihr.ac.uk/evolving_the_network

107 NIHR Clinical Research Network website: Commercial study costing templates page. www.crncc.nihr.ac.uk/Life+sciences +industry/tools/costing

108 NIHR website: Model Agreements. www.nihr.ac.uk/industry/Pages/model_clinical_trials_agreement.aspx

109 NIHR Clinical Research Network website: Objectives. www.crncc.nihr.ac.uk/about_us/ performance_objectives

110 NIHR Health Technology Assessment website: MAGnesium NEbuliser Trial In Children (MAGNETIC) study record. www.hta.ac.uk/id=1615

111 International Standard Randomised Controlled Clinical Trials Number (ISRCTN) reference for the MAGnesium NEbuliser Trial In Children (MAGNETIC) study. www.controlled-trials.com/ ISRCTN81456894


• A source of important information on Enpr-EMA.