

## The Medicines for Children Research Network: building on current success as we move forward

The National Institute for Health Research (NIHR) Medicines for Children Research Network (MCRN) was established in 2005, in response to the European Union Paediatric Regulation. Subsequently the Paediatric (Non-Medicines) Speciality Group (PSG) was set-up in 2009 as part of the NIHR Comprehensive Clinical Research Network to support a national portfolio of paediatric research studies that do not involve medicines. After 9 years in operation, the NIHR Clinical Research Network has been undergoing reconfiguration and from April 2014 the two portfolios, of MCRN and PSG, have come under combined management of the NIHR Clinical Research Network: Children's Theme. The formation of the Children's Theme provides an even greater opportunity for healthcare professionals and all those working in this field to collaborate to strengthen still further the delivery of children's research as the new theme is taken forward. This update will outline the achievements of the NIHR MCRN and the PSG to date; and will describe the vision for supporting children's research that will form part of the transition to the reconfigured Network.

**Keywords:** children • clinical trials • Enpr-EMA • EU regulation • medicine • network • paediatric • research

### Background

Research in children and young people requires the need to balance the many and complex requirements of scientific inquiry, regulatory authorities, ethics committees, the pharmaceutical industry and, most importantly, children and families. Aspects such as involvement of children, young people and carers in research design and priority setting [1]; resources to enable paediatricians to undertake research [2] and participation of community centers [3] have been highlighted as challenges and areas requiring specific attention. Paediatric drug development trials in particular have been historically challenging due to a obstacles such as ethical concerns, recruitment problems and consent issues [4,5]. This was compounded by the reluctance of pharmaceutical companies to develop drugs in what is perceived to be a small, non-rewarding paediatric market. A large number of existing medicines used for children have not been studied adequately in a paediatric

population and the result has been widespread use of off-label and unlicensed drugs for children [6,7]. With distinct physiological and psychological differences existing between children and adults, responses to treatment in children are unpredictably different to adults [4,5]. Studies examining the link between drug use and adverse drug reactions have had differing results; with many suggesting a greater adverse drug reaction risk associated with off-label and unlicensed drug use [6,8]. In response to these concerns The European Union Paediatric Regulation ([EC] No 1901/2006; [EC] No 1902/2006) came into force in January 2007, with objectives to increase the availability of medicines intended for children; to make information on those medicines widely available and to stimulate high-quality paediatric research [9].

Simultaneously, in England, the Department of Health (DoH) and Medicines and Healthcare Products Regulatory Agency

Sabah G Attar<sup>\*1</sup>, Vanessa Poustie<sup>1</sup> & Michael W Beresford<sup>1</sup>

<sup>1</sup>The National Institute for Health Research Children Research Network: Children, University of Liverpool, Department of Women's and Children's Health, Institute of Translational Medicine (Child Health), Alder Hey Hospital, Liverpool, L12 2AP, UK  
\*Author for correspondence:  
Tel.: +44 151 252 5067  
sgattar@liverpool.ac.uk



(MHRA) responded by developing a pediatric strategy in 2004 [10]. This resulted in the establishment of a national pediatric network within the National Institute of Health Research (NIHR), the NIHR Medicines for Children Research Network (MCRN) in 2005. The Network realizes the potential of the NHS by being embedded within it; and provides an efficient and well-organised framework for the conduct of studies funded by public funding bodies and the pharmaceutical industry [11]. In 2009, the Paediatric (Non-Medicines) Specialty Group (PSG) was set-up as part of the NIHR Comprehensive Clinical Research Network (CCRN) to support a national portfolio of research studies in pediatrics for those studies that do not involve medicines. This element of the Network received infrastructure support from within the CCRN. However support for non-medicines research in children through the national networks has been varied until now and has not received the same prioritization or resources as medicines research. There have been calls that children's research will be more efficient and better served, by a fully-funded, unified NIHR Network that supports both drug studies and non-medicines pediatric studies [2]. NIHR Clinical Research Network (CRN) has been undergoing widespread and significant reorganization to improve still further access for researchers, to harmonize and simplify processes in order that the quality of research support and delivery can be further improved [12]. Since April 2014, the two portfolios, of MCRN and PSG, have come under combined management of the NIHR CRN: Children's Theme. This enables best practice and the current highest level of services to be provided and maintained across all children's research in the new structure. In light of the recent focus within DoH on research in children and young people [13,14], reorganization will improve the Network support available across all of England for both medicines and non-medicines studies involving children. Although specifically focused on England, the NIHR CRN: Children's Theme will continue to work extremely closely and collaboratively with corresponding networks within the UK's Devolved Nations.

### Achievements Research portfolio

Since its establishment in 2005, the MCRN has developed a diverse portfolio of studies. This has primarily been the responsibility of the 15 NIHR MCRN Clinical Studies Groups (CSGs), which between them cover all pediatric specialities. These national groups are each chaired by a distinguished research leader of international standing and have multidisciplinary membership including clinicians, research nurses,

pharmacists, basic scientists and parent/carer representatives. Some of the groups have developed close links with relevant funding bodies/patient support charities. Their role includes identification of research priorities, to give specialist and methodological advice to investigators and to review feasibility of the studies to be included into the portfolio.

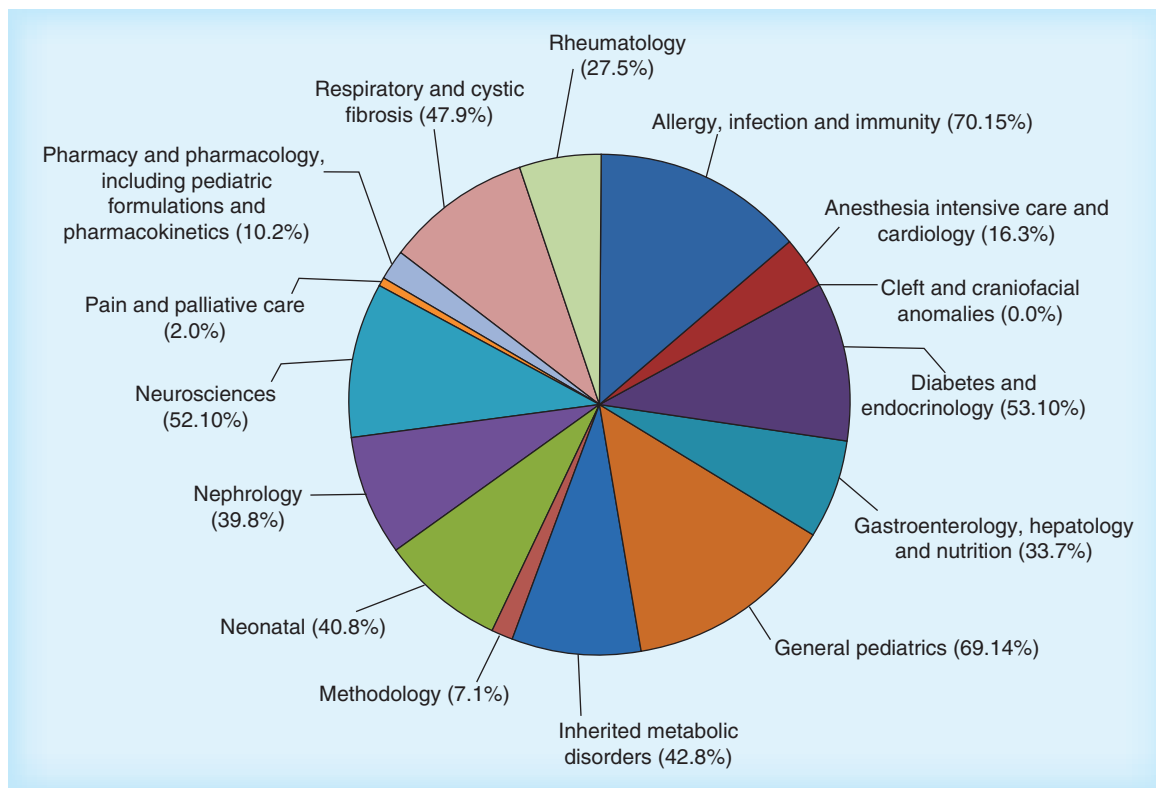
As of February 2014, the MCRN portfolio contained 507 studies that cover all subspecialties represented by the CSGs (Figure 1), 195 of which are open to recruitment or in setup. The majority of the studies are interventional with over 40% being randomized controlled trials.

The MCRN commercial study portfolio has grown rapidly since 2006 and now represents 56% of all studies supported by the MCRN (Figure 2). These data can be contextualized with the increase, albeit moderate, that has been reported for pediatric trials across Europe, in the 6 years since the EU Paediatric Regulation came into force [9]. The number of industry studies that the MCRN has been approached to support (748 to date) strongly indicate that the EU Paediatric Regulation has led to a fundamental change in the approach that companies are taking to develop more child-appropriate medicines.

Whilst the PSG was formed at a later stage, since 2009 its portfolio of supported studies has grown rapidly, supporting a total of 580, of which 312 studies as main research network and 268 as supporting network as of February 2014. This portfolio includes studies on screening, diagnosis and the development of prognostic tools including imaging; non-medicines interventions such as behavioral interventions and medical devices; studies on normal development and the pathogenesis, monitoring and prevention of disease; cohort studies and the effect of lifestyle factors such as diet, nutrition and exercise. With only two commercial studies in the PSG portfolio to date, there are opportunities to significantly increase commercial participation in non-medicinal pediatric research across the UK.

### Recruitment & delivery

The network continues to provide a comprehensive range of support services to companies and non-commercial investigators. These include guidance on EU regulations, advice on protocol development, consumer involvement in research and local research network staff assisting in set-up and recruitment whilst the trial is underway. Network staff work with sites and sponsors to ensure that studies are conducted rapidly and to a high standard. Recruitment of participants to MCRN studies has increased to approximately 10,000 participants on an annual basis by 2013–2014; and to almost four-times that for the PSG. Between the PSG



**Figure 1. Medicines for Children Research Network studies included into each of the Clinical Studies Groups portfolio, February 2013.**

and MCRN studies the Network has supported the recruitment of more than 270,000 participants into clinical trials involving children to date (Figure 3).

The support provided by the Network has impacted positively on study performance, with more than 70% of MCRN studies recruiting to time and target consistently for the studies closing in the last 3 financial years (Figure 4) and approximately 30% of international multicenter commercial studies recruiting their first participant in the UK [11].

The number of sites involved in MCRN studies across England has increased year-on-year. The increase in secondary care sites is encouraging (60% increase between the financial years 2007–2008 and 2012–2013; Figure 5) considering the historic tendency for pediatric research to be centered within the main tertiary teaching hospitals, whilst there is a large population of children with general conditions who are seen predominantly in the district general hospitals and primary care setting [3]. There are notable examples within MCRN supported trials, of district general hospital clinicians excelling in large multinational commercial trials (Box 1 is a case study on one such example). Further to this, strong links have been fostered with the NIHR Primary Care Research Network since its development, through joint meetings and sharing of best practice at both local and national

levels, which has enabled effective delivery of jointly supported pediatric trials.

Network staff also work in close collaboration with NIHR's Paediatric Clinical Research Facilities (CRFs) to support both commercial and non-commercial research. There are more than 16 children's CRFs in the UK that support high-intensity studies, including pharmacokinetic and pharmacodynamic research [15], which establishes a strong platform to deliver the Children's Theme research across the primary, secondary and tertiary centers in the country.

### Working across Europe

The EU Paediatric Regulation required the European Medicines Agency to develop a European network of existing national and disease-specific networks, investigators and centers with specific expertise in the performance of studies in the pediatric population. The aims of the, now established, European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) are to promote high quality research, by strengthening collaboration among high quality networks, and facilitate communication, build competencies and define scientific and operational quality standards through application of rigorous recognition criteria [16]. As a member of Enpr-EMA since its inception, MCRN has had an opportunity to foster research

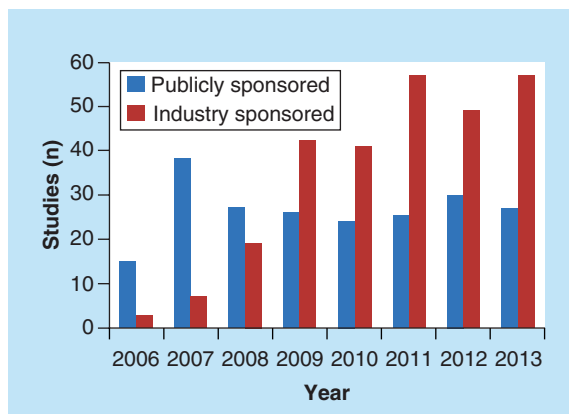


Figure 2. Number of studies included into Medicines for Children Research Network Portfolio each year.

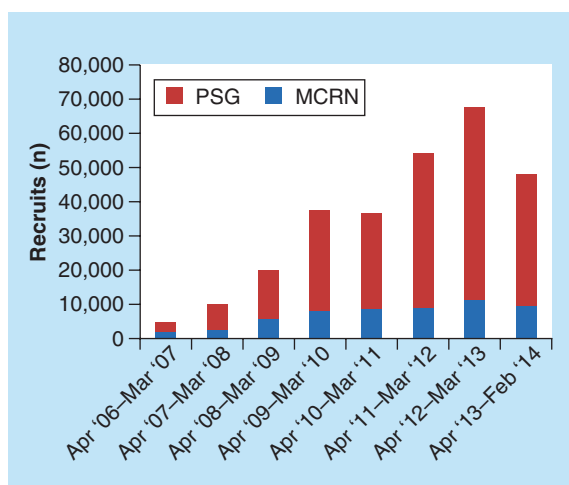


Figure 3. Annual recruitment to Medicines for Children Research Network Portfolio and Paediatric (Non-Medicines) Specialty Group supported studies across England.

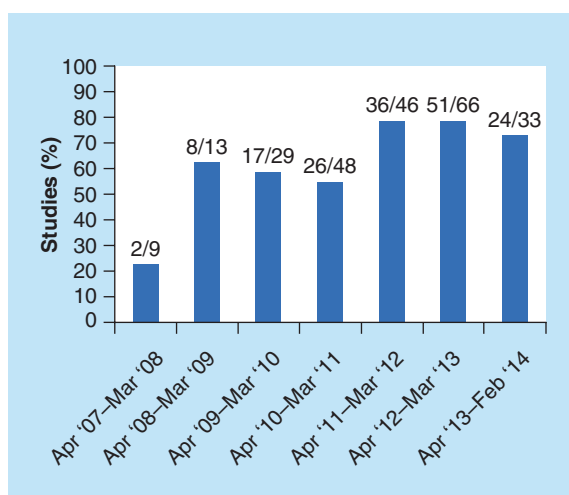


Figure 4. Percentage of studies achieving 100% recruitment to target.

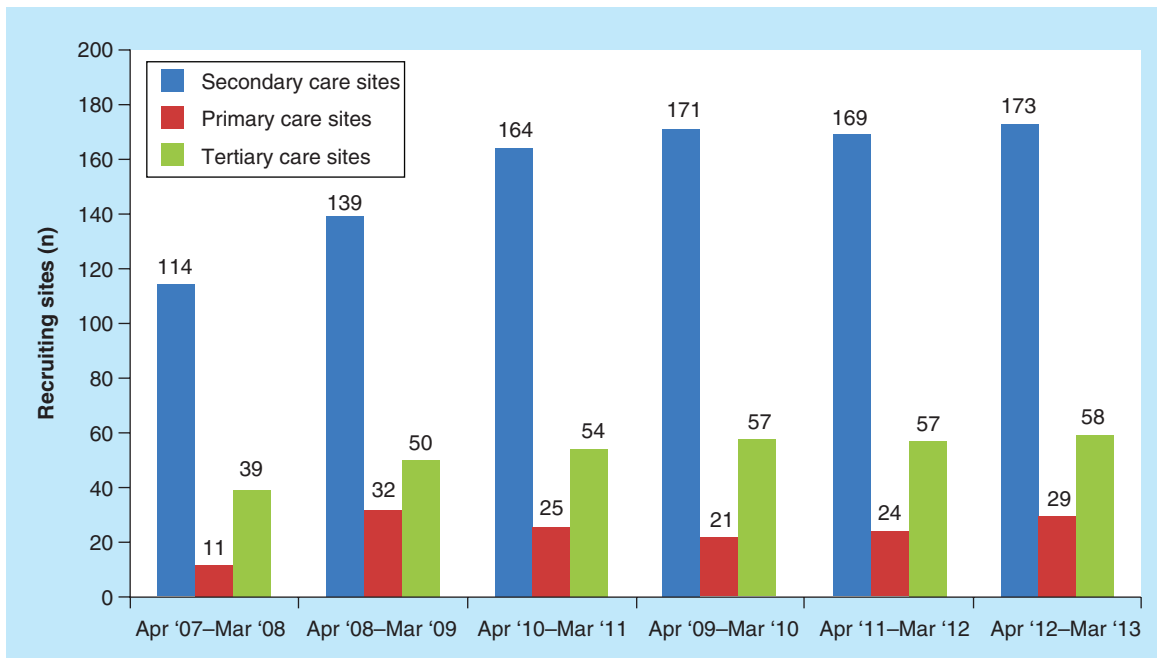
on medicinal products for use in children through efficient internetwork and stakeholder collaboration. MCRN has worked closely with its constituent networks to share best practice; to provide advice on studies and programs and to identify research centers.

### Children & family input into research

The MCRN has a very effective strategy with a clear remit of involving children and parents in all key aspects of the research process. There was little baseline evidence concerning the previous actual contribution of service users and carers in health research, to the design of randomized controlled trials [1]. This was despite the UK's DoH's strong recommendations for encouraging it [17]. Therefore this was and remains a key strategic priority for the MCRN. Indeed, children and carers involved in MCRN's national groups have collaborated with investigators at varying levels on more than 100 studies since 2006. MCRN has been innovative in its approach, which has led to improvements in the quality of patient information, the design of studies to improve their delivery and changes to national guidance [18]. Keeping abreast of European and international initiatives regarding ethical conduct of children's research, MCRN has worked in partnership and shared best practice with Royal College of Paediatrics and Child Health, EnPrEMA and on initiatives such as STAR Child [19]. The recent GenerationR event, which was largely designed and hosted by the children and young people of the MCRN's national groups, showcased how children and families have contributed to design and delivery of research; whilst working with global pharmaceutical industry [20].

### Working with the pharmaceutical industry

The growth of the industry portfolio and international successes of sites involved in MCRN commercial trials have been highlighted above. In addition to responding to requests to advise on/support studies, the MCRN supports initiatives to enhance the services that it offers. The establishment by MCRN of the Children's Research Industry Group is one of these new initiatives to improve collaboration with and services offered to pharmaceutical companies and Contract Research Organisations. The Children's Research Industry Group links MCRN and other organizations (including Children's CRF), with representatives in industry working on children's medicines, devices and other areas. This group provides a forum for the discussion of children's research issues and to attract additional studies to the UK and will allow the Children's Theme and other affiliated organizations to obtain advice on industry matters.



**Figure 5. Number of sites recruiting to Medicines for Children Research Network studies between 2007 and 2013.**

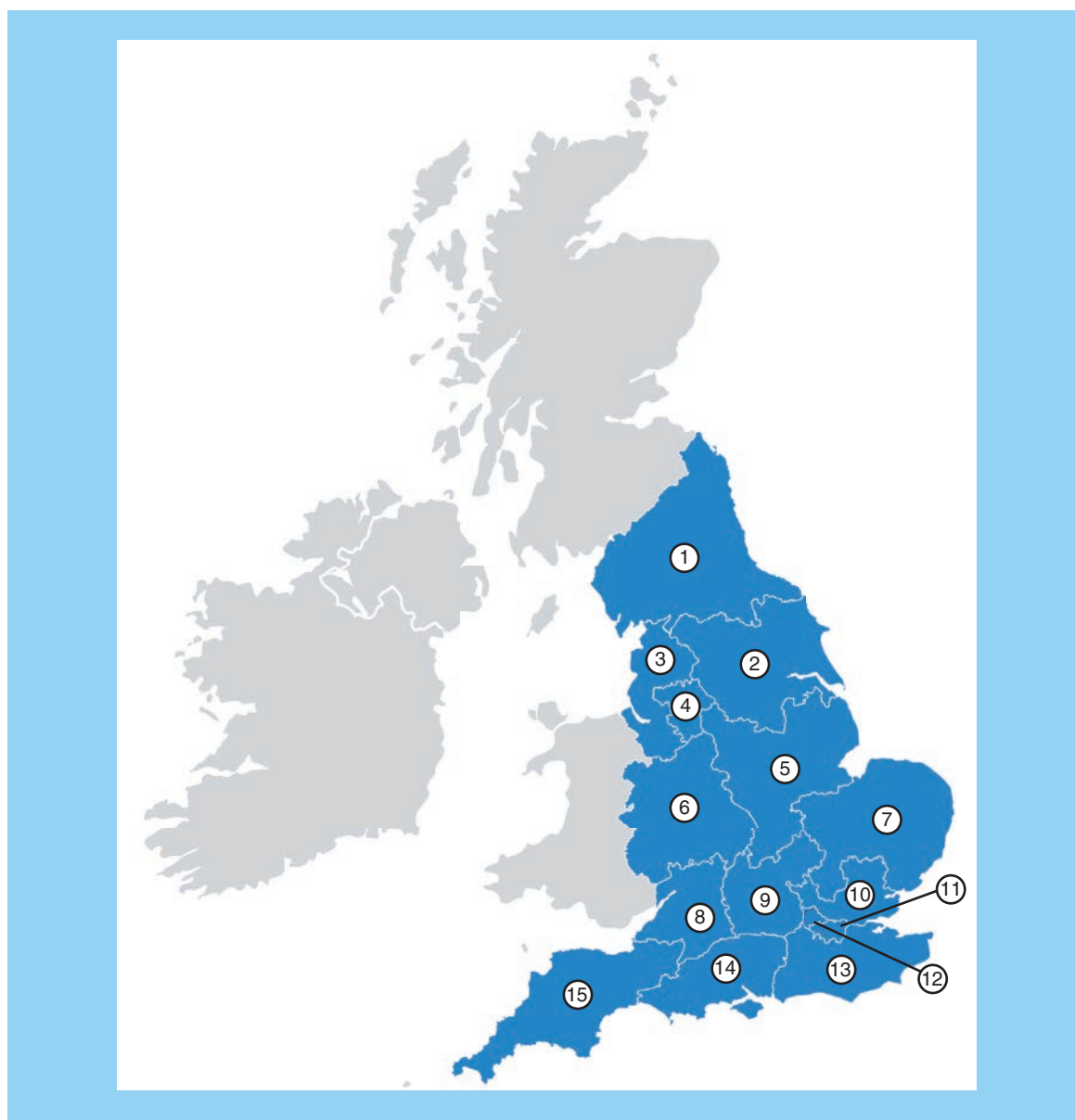
### Future perspective

With the alignment of MCRN and PSG under the new NIHR CRN: Children's Theme, and the reconfiguration of the whole of the NIHR CRN, delivery of all studies supported by the Children's Theme will be through 15 Local Clinical Research Networks (Figure 6), which will be nationally coordinated. Each Local Clinical Research Networks will contain clinical leadership and multidisciplinary teams dedicated to the conduct of pediatric trials, whilst allowing the alignment of resources/workforces to be maximized at local and national levels. Whilst simplifying the structures for investigators and funders, the Children's Theme will ensure equity of access for all pediatric patients within England. It will also enable increased sharing and simplification of processes and a unified voice in the engagement of key national and international stakeholders.

These changes coincide with the recent publication of the 2012 Annual Report by the Chief Medical Officer of England [13], which focused specifically on child health and placed prevention at the heart of its recommendations. There are a number of key recommendations within the Report that refer to Public Health England employing an evidence-based approach towards initiatives and assessment of interventional programs for children and young people. Furthermore, a recent All-Party Parliamentary Group meeting on Medical Research (6th November, 2013) addressed the topic of children and young people in medical research as a round-table discussion including senior representation from the MCRN. The discussion identified research as a key tool that can have a significant impact on children's health and encouraged processes to be put in place to increase opportunities for young people to be involved in

#### Box 1. Case study of Johnson & Johnson's Proton Pump Inhibitor for Gastro Osophageal Reflux Disease study at Barnsley District General Hospital.

- Johnson & Johnson were keen to base their sites at large teaching hospitals with a history of supporting commercial research
- Medicines for Children Research Network East Local Research Network however, confident that the team at Barnsley (UK) could recruit to time and target, convinced Johnson & Johnson that Barnsley District General Hospital could make a valuable contribution
- In the absence of a pediatric research nurse at Barnsley, Medicines for Children Research Network East Local Research Network nurse support proved invaluable to the study by providing hands-on support at different stages of study delivery and providing Johnson & Johnson with a single point of contact for information
- One of 17 sites throughout the world, the Barnsley team met their target of three patients, and they went on to recruit five patients in total and become one of the leading recruiters in the world.



**Figure 6. The 15 Local Clinical Research Networks.**

research [14]. Within this context, the NIHR CRN Children’s Theme is effectively and strategically positioned to strongly support the development and delivery of research programs to help meet this need over the next few years.

The bringing together of both MCRN and PSG has resulted in a new and combined portfolio of children’s studies with a wide range of differing characteristics that will be carefully managed with the Children’s Theme portfolio. Importantly, there is a requirement to maintain (and indeed exceed) the highest levels of portfolio management and support within the combined portfolio. This will be led by the current MCRN National Coordinating Centre hosted at Alder hey Children’s

NHS Foundation Trust by the University of Liverpool (Liverpool, UK). The future presents an exciting opportunity to build on the experience, expertise and success developed over the last 9 years, strengthening still further collaborations with industry and the widely acknowledged work with children and carer representation in research that can support all areas of children’s research.

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**Executive summary**

- From its formation in 2005 until the present day, the National Institute for Health Research (NIHR) Medicines for Children Research Network (MCRN) has recruited 56,000 participants into over 450 pediatric studies.
- The Paediatric (Non-Medicines) Speciality Group, set-up in 2008 as part of the NIHR Comprehensive Clinical Research Network to support a national portfolio of pediatric research studies that do not involve medicines, has recruited over 222,000 participants in over 500 pediatric studies.
- Since April 2014, the two portfolios, of MCRN and Paediatric (Non-medicines) Speciality Group, have come under combined management of the NIHR Clinical Research Network: Children's Theme, with best practice and current services provided being maintained in the new structure.
- The Network continues to build on the high level of support provided to companies and non-commercial investigators with regards to guidance on EU regulations, advice on protocol development, consumer involvement in research and Local Research Network staff assisting in trial set-up and recruitment.
- The Network has had great successes with collaboration with industry; European initiatives and the work on children and carer representation in research since the inception of the MCRN; and is effectively positioned to support the development and delivery of research programs across all of pediatrics over the next few years.

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