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Supporting neonatal research – the Medicines for Children Research Network

There is a distinct lack of information regarding medicine appropriate for administration to children, particularly neonates. This article describes the Medicines for Children Research Network and the Extended Neonatal Network, including a summary of how the networks fit in with the recent changes in the way that the NHS supports neonatal research in the UK. These new initiatives should help to fill the information gap.

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Key points

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1. The Medicines for Children Research Network(MCRN) and the Extended Neonatal Network have been set up to encourage high quality research in neonatal units.
2. In future money that Trusts receive from the NHS for research will be tied to specific projects adopted by the MCRN and similar organisations.
3. Research will need to meet guidelines for Good Clinical Practice.
4. All new medications licensed in Europe now have to be tested in children of all ages, unless the pharmaceutical company applies for a waiver.
5. The new initiatives should help to redress the dearth of relevant information about medicines for infants, particularly neonates.

Many people who look after newborn babies are enthusiastic about research. The Medicines for Children Research Network (MCRN) aims to focus that enthusiasm on an important clinical problem – the limited amount of information available concerning medicines given to children. An important element of the MCRN is the Extended Neonatal Network (ENN – neonatal@mcrn.org.uk). This article starts by reviewing the rationale for the MCRN and ENN, answers some key questions about the network and describes how people can get involved in research through the MCRN and the ENN. This subject is an area of rapid change and this article describes the situation at the time of writing. The focus is on England, with some comments on the situation in the devolved nations of Scotland, Wales and Northern Ireland.

Background and rationale

The MCRN and ENN have been set up to meet the challenges of the evolving research landscape. There are two main ways that the research landscape is changing: organisational and legal.

Organisational changes

The UK government has recently reconfigured research and development (R&D) in the NHS. NHS R&D aims to deliver improved health care for the UK by making sure that good research is completed efficiently. The Department of Health has set up the United Kingdom Clinical Research Network (UKCRN) to oversee this reconfiguration and to ensure that the aims of the Government's health research strategy are met. The UKCRN has set up six topic specific research networks (including the MCRN) and 25 comprehensive local research networks (CLRNs). MCRN was asked to develop local research networks (LRNs). These were set up in 2005 in six regions that provided strong cases for collaborative research. The MCRN LRNs cover 60% of children and young people in England. There are similar groups in Scotland, Wales and Northern Ireland. Given the strong tradition of research on neonatal units, an extra network for neonatal units has been set up – the Extended Neonatal Network (ENN).

Part of the reconfiguration of R & D in the NHS is reallocation of resources. In the past each Trust was given money to support R&D, although it was unclear how efficient this was and money was often spent on patient care. In future money will be spent directly on research through funding schemes that support specific projects or that train researchers (such as nurses and allied professionals). Money for research infrastructure will be allocated according to performance in meeting research targets. The most important targets relate to recruitment to studies that are in the UKCRN research portfolio.

In the past many Trusts were able to support research from money they received from the NHS R&D Levy. The NHS R&D levy is being withdrawn. In future, money that Trusts receive for research will usually be tied to specific projects that have been funded by an outside body. It will be very difficult to do research without getting external funding and without help from a range of people. The MCRN and ENN have been set up to help researchers develop fundable projects and to help people do research. However, the MCRN will be judged on how efficiently it helps with recruitment to studies within the portfolio. This means that research studies

that units fund themselves (e.g. from Endowment funds) will not receive help from the MCRN and ENN.

Research is funded by a range of organisations: MRC, Wellcome Trust, charities etc. and usually includes 'direct costs' – salaries of people who do the research, and immediate costs of research, such as medicines used in trials. In the past the NHS has also funded some 'backup costs', or "service support costs", which include the investigations (pathology and imaging) that are done during a study as well as the cost of pharmacy work that is similar to routine pharmacy work. In future, service support costs will only be available for projects that have been adopted in the UKCRN portfolio. Previously Trusts used the NHS R&D levy to subsidise service support costs for their 'own-account' research, such as that funded by Endowment funds. In future Trusts are unlikely to provide this support.

Legal changes

One important legal change dates from 2004. Since 2004 there has been a legal requirement to conduct research involving medicines in line with regulations issued by the UK Medicines and Health Care Products Regulatory Authority (MHRA). These regulations are based on guidelines about Good Clinical Practice (GCP) in Research issued by the International Commission for Harmonisation. GCP is designed to protect patients and maximise the quality of trials. High quality research is more reliable than other research. Although GCP has been around for a while, it has become increasingly prominent as the MHRA has started to conduct detailed inspections of hospitals across the UK. The requirements of GCP may appear onerous, but can be met with multidisciplinary support, including support from the MCRN.

The second important legal change is the European Regulation on Medicines for Children which came into force in January 2007. This regulation is designed to improve the quality of medicines available to children by ensuring that all new medications are tested in children of all ages including newborn infants of all gestational ages. Before any new medicines can be licensed in Europe the manufacturers will need to develop a Paediatric Investigation Plan (PIP) to include details for testing medicines in newborn infants. If a medicine is clearly not going to be used in newborn babies the manufacturers can apply for a waiver. At the time of writing the list of automatic waivers is limited to around 15 conditions and so most medicines will need to be tested on children and newborn babies. To date, the pharmaceutical industry has indicated that it will apply for at least 500 PIPs. Many of these will involve testing new medications on neonates. The MCRN and ENN will be the 'clearing house' for these studies.

What is the ENN?

The ENN includes 80 neonatal units at the time of writing. At present the ENN is open to all neonatal units in England. The MCRN includes Scotland, Wales and Northern Ireland, and the ENN is keen to collaborate with colleagues in the devolved nations, although currently only units within England have been invited to join the ENN. The aim of the ENN is to facilitate all units to join in with research that addresses important questions in the provision of neonatal care. Support from the ENN relates mainly to large scale randomised controlled trials that need to be done well and completed quickly. The ENN is funded by the MCRN and coordinated by the National Perinatal Epidemiology Unit based at the University of Oxford (www.npeu.ox.ac.uk/neonatalnetwork).

How does the ENN help with research?

The ENN helps set up and run studies in a number of ways (**FIGURE 1**).

For individual neonatal units, this help includes:

- Informing units about studies with which they can get involved.
- Support with getting approvals from the Ethics Committee and Trust Research Department in each hospital involved in a study
- Supporting staff when they start to get involved in each study
- Closing down projects efficiently when recruitment is complete
- Indicating what support is required for each study e.g. pharmacy.

As well as helping with specific research projects, the ENN also provides more general support including information about potential sources of funding for new studies, advice about how to apply for approvals and funding, and up-to-date information about training opportunities. All units in the ENN are sent a quarterly newsletter, with information on relevant issues including an update on planned, ongoing and recently completed neonatal studies within the UKCRN portfolio.

MCRN has a Consumer Liaison Officer who ensures that all important decisions made by MCRN and its components have been reviewed by children, parents and carers. Before a study can be part of the MCRN portfolio it will ideally have been reviewed by several consumers.

Which neonatal studies are the MCRN and ENN currently involved with?

An up-to-date list of portfolio studies and contact details for each study can be found at http://pfsearch.ukcrn.org.uk/Topic.aspx?TopicID=4 (**TABLE 1**). The portfolio is the collection of studies that have been funded following national peer review and then reviewed for quality and relevance to children and newborn babies. In future,

Acronym	Title	Status	Type	Open to additional sites
ADEPT	Abnormal Doppler Enteral Prescription Trial	Open	Interventional	Yes
BOOST II UK	Which oxygen saturation level should we use for very premature infants? A randomised controlled trial	Open	Interventional	No
INIS	International neonatal immunotherapy study	Open	Interventional	No
NEST	Neonatal ECMO study of temperature	Open	Not specified	No
TIPIT	A randomised controlled trial of thyroxine in preterm infants under 28 week's gestation	In set-up	Interventional	Yes

TABLE 1 Major ongoing neonatal trials in the MCRN portfolio (http://pfsearch.ukcrn.org.,uk/Topic.aspx?TopicID=4).

the NHS will only give financial support to studies within the portfolio. Most of these studies are about finding out which treatments work. Some studies are about licensing new and existing medicines, to provide information about safety and enable the regulators to deal with any problems that arise when medicines are used in newborn infants. Other studies are not trials of an intervention but are designed to improve the way that medicines are used.

What about formulations?

Many of the formulations of medicines used in newborn babies have not been tested properly. Improving formulations and testing them properly is a priority for the MCRN. Three formulation scientists have been employed by MCRN and they will be working on this important area.

What about research that does not involve medicines?

The MCRN helps with studies that look at prevention and diagnosis as well as treatment, for example feeding and cooling. Research that does not fall within the remit of MCRN will be the responsibility of the UKCRN and its comprehensive local research networks.

Why do we need the MCRN and ENN?

Everybody who has been involved in research will recognise the difficulties of doing research. The MCRN aims to reduce the obstacles associated with carrying out research and make sure that the protocol answers the research question and is feasible. It can also help sort out research governance issues and smooth the rough corners of research such as follow-up when babies are moved between hospitals. Obstacles to research seem to have increased recently because of initiatives designed to improve the quality of research (see Organisational and Legal changes above). The MCRN and ENN have been established in order to make sure that neonatal units and researchers can adapt to these initiatives. The MCRN and ENN also monitor recruitment to each study and can enlist extra units if need be (**FIGURE 1**).

How do the MCRN and ENN help develop research?

The MCRN has established 11 Clinical Studies Groups (CSGs). One of these deals with neonatology and is able to review protocols and ensure suitable multi-disciplinary input (statisticians, pharmacists, parents and carers etc.). The Neonatal CSG provides thorough peer-review of a study protocol by experienced neonatal researchers. This peer-review focuses on the quality of the study and can point out problems the investigators may encounter. When planning research, it is important that this facility is accessed as soon as possible, for example when the first draft of the protocol has been prepared. Approval by the Neonatal CSG is likely to increase the chances of support by a funder, although different funders recognise CSG approval in different ways. In future, the number of proposed studies may be greater than the capacity of the network. The Neonatal CSG is working towards transparent and equitable ways to prioritise proposed studies.

Once a study has been reviewed by the CSG and funding has been obtained based on national peer-review, it is reviewed by the Study Adoption Committee (SAC). The SAC gives advice about ethical and clinical aspects of the study and the practicalities of rolling out the study across the MCRN/ENN, before deciding whether it should become part of the MCRN portfolio.

Does the MCRN provide training about research?

The MCRN runs a range of courses about research in children. The UKCRN also runs other courses that are useful for people doing research. Details of these courses can be found at: www.ukcrn.org.uk.

Does the MCRN fund research?

The MRCN does not fund research, but there are lots of other groups and

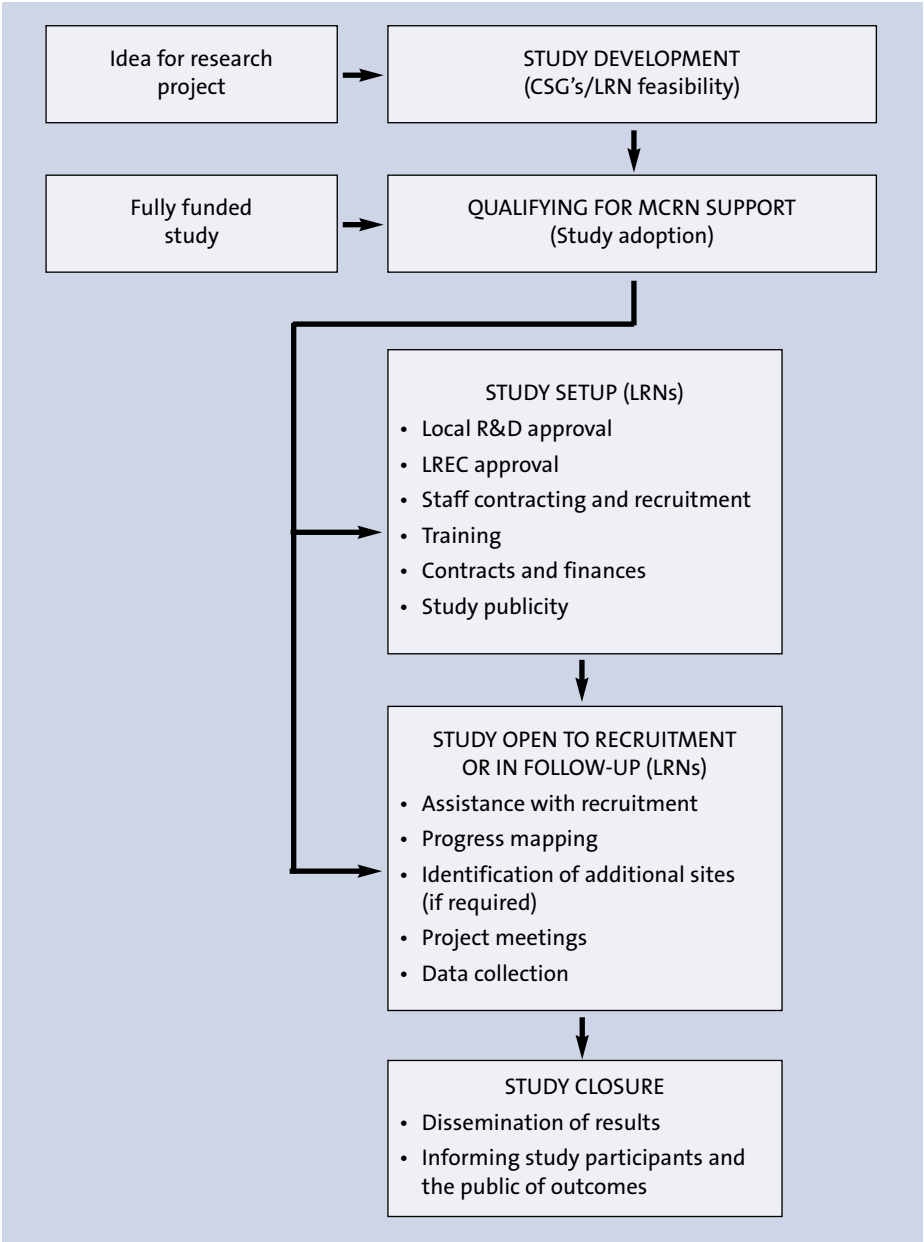

FIGURE 1 Flow diagram to illustrate the support that MCRN and the ENN can provide.

organisations that do provide funding. However, research in the NHS involves costs that can sometimes be hidden and are not usually paid for by charities and other groups that fund research. The MCRN can provide practical help with parts of the research process that are often not funded and can help with some aspects of developing a bid for funding.

Does the MCRN have links with industry?

MCRN has links with industry in order to meet its aim of ensuring research funded by the pharmaceutical industry can be done quickly and cost-effectively, if it is relevant to the needs of children. In the past, the pharmaceutical industry has been less involved in research about newborn babies than in other groups. This situation is likely to change because of the recent changes in European law already discussed, which are designed to improve the information available about medicines used in children.

Getting involved

There are several ways that staff and units can get involved in the work of the MCRN and ENN. Staff can contribute to existing research, by recruiting to one of the portfolio studies or by helping with the follow-up of babies who have been recruited to a study at another unit and then transferred to their unit. In addition, there are lots of areas of neonatal care that need research, especially issues related to the use of medicines. Staff can help with the organisation of research within their unit by being the link-person with the MCR /ENN. The role of the link-person is not limited to doing research.

One important role of the network is to examine the feasibility of proposed research projects. As research projects are developed, individual units will be asked whether specific studies could be done on their unit. For example, the ENN will ask units for numbers of patients with a specific condition. A rapid response to these requests will be important, particularly for studies that are proposed by the pharmaceutical industry. Members of the neonatal CSG are selected every three years. Staff with experience of research, as a nurse, doctor or other healthcare professional, may wish to apply for membership of the CSG. Service-users/consumers are always needed for meetings of the CSG and other groups. Staff involved in trials on the MCRN portfolio can attend training courses about research.

Conclusion

For many years people who look after babies have complained about the lack of relevant information about medicines. Recently, changes in the legal framework and the way the NHS is organised have provided a great opportunity to fill that information gap. The MCRN and ENN provide the tools to do the necessary research. Now is the time to get involved and make a difference.

Note

Dr. Turner is a member of the Executive Committee and Board of the national co-ordinating centre of the MCRN. This article has been reviewed by members of staff at the co-ordinating centre. However, the views and interpretations expressed in this article remain the responsibility of Dr. Turner.

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