NIHR Medicines for Children Research Network response

Introduction

The National Institute for Health Research (NIHR) Medicines for Children Research Network (MCRN) is part of the National Institute for Health Research Clinical Research Network (NIHR CRN), and forms part of the UK Clinical Research Network. The Networks support and deliver high quality clinical research studies.

The MCRN has been created to improve the co-ordination, speed and quality of randomised controlled trials and other well designed studies of medicines for children and adolescents, including those for prevention, diagnosis and treatment.

The Network has extensive knowledge and experience of paediatric research, and supports publicly-funded/NHS-sponsored, pharmaceutical/biotech-sponsored and investigator-initiated partnership studies in over 100 NHS sites that serve approximately 6 million children. The MCRN supports studies though its infrastructure, which includes the MCRN Coordinating Centre, Local Research Networks (LRNs), Clinical Studies Groups (CSGs), Clinical Trial Units (CTUs) and a Neonatal Network.

The MCRN Coordinating Centre is led by a consortium comprising the University of Liverpool, Alder Hey Children's NHS Foundation Trust, Imperial College London, National Perinatal Epidemiology Unit (NPEU; University of Oxford), Liverpool Women's NHS Foundation Trust and the National Children's Bureau.

The MCRN very much welcomes this consultation and wishes to contribute its response to aspects of the consultation which are relevant to paediatric research.

Response to the Clinical Trials Directive Consultation from the NIHR Medicines for Children Research Network (NIHR MCRN)

The table below includes our comments on generic issues that will apply to both paediatric and non-paediatric clinical trials of investigational medicinal products (CTIMPs).

Many of these issues have been encountered in NIHR MCRN studies. Whilst not specific to paediatric trials, it may be argued that some occur more frequently, or are perceived to be more burdensome in MCRN studies as a result of some or all of the following: lesser involvement of individuals with paediatric expertise at various stages in the process, smaller research evidence base, less commercial interest and more limited Clinical Trials Unit involvement in paediatric trials than other areas.

The NIHR MCRN fully supports the new EU Paediatric legislation and wishes there to be no barriers across EU member states to its implementation.

The aim of the rest of this paper is to respond to the specific questions posed to MCRN identifying issues particular to paediatric CTIMPs. There are clearly some design/conduct features that will be paediatric-specific e.g. consent/assent, choice of outcome measures, but many that are not e.g. need for appropriate sample size. If we are going to recommend the use of particular drugs in children, or abandon their use, the quality of the evidence on which this is based has to be at least as robust as

it would be in adults. Paediatric-specific issues are only identified below if considered to be problematic in relation to the implementation of the CTD.

Specific aspects relevant to MCRN

1) Does the Directive adequately provide for undertaking trials in different settings and with different groups of trial participants?

We identify five issues of concern.

(i) Issues of GCP training/staff documentation in settings such as A&E, NICU, PICU, shared care paediatric oncology sites

There is widespread uncertainty in the UK about who requires GCP training in the clinical setting of a non-commercial trial where the intervention being used is an established or low-risk intervention. For example, one trial is recruiting babies less than 32 weeks gestation at birth and giving them probiotics or placebo, from day two after birth until 36 weeks gestation. The drug is given daily as an oral dose and the risk of adverse consequences arising from the administration of the product or placebo is extremely low. The number of neonatal nurses who will be giving the drug to the baby will be large – potentially every member of the nursing staff within a particular neonatal unit. Do all of these nurses need GCP training for the purposes of giving a simple non-toxic medicine? If so, the burden to the participating centres will be substantial. We would argue that by restricting this activity to a relatively small number of nurses, it is likely that there will be significant periods of non-compliance with protocol because there is nobody sufficiently trained to administer the drug. The results of the trial will therefore be invalid.

(ii) Trials of emergency medicines for children

The clinical and ethical requirements for conducting trials of emergency medicines are as equally important for children as for adults and as for non-emergency medicines. In the UK it is now legal to undertake paediatric trials in emergency settings with deferred consent. We support a revision of the system across EU and encourage consideration of UK solution by other Member States.

(iii) Recruitment of participants into more than one trial at the same time

This issue arises relatively often in neonatal intensive care in the UK. Our view has been that if there are no scientific reasons not to recruit simultaneously to two or more trials, then parents should be given the option to consider participating in more than one study. There appears to be, however, confusion amongst ethics committees, the pharmaceutical industry and investigators about whether this approach is, or is not, acceptable and there is no guidance within the existing Clinical Trials Directive.

(iv) Longterm pharmacovigilance

Most pharmacovigilance is relatively short term and will identify unlikely or unusual events. However, in the neonatal population, particularly those born preterm, the manifestations of adverse events are extremely limited. For example, preterm babies cannot mount an allergic response. The adverse consequences of a new therapy therefore manifest as general signs of ill health which are almost impossible to separate from the consequences of prematurity. Identifying SUSARs in this situation

is almost impossible, and becomes relatively meaningless. However, and of much greater significance, is the potential long term consequences of exposure to drugs. Although the ORACLE Trial exposed fetuses in-utero to commonly used antibiotics to treat preterm labour or prelabour rupture of the membranes, the long-term follow-up this group at the age of seven years demonstrated an increased risk of neurodevelopmental delay and cerebral palsy in the group exposed to erythromycin compared with those exposed to placebo. These consequences would not be detected by standard pharmacovigilance methods, nor by interrogating routine data systems, as these important neurodevelopment outcomes are not captured by these systems. By focussing activity and time on short-term pharmacovigilance, which for generic drugs widely used in clinical practice is unlikely to yield any useful information, there needs to be a change in emphasis to how we measure long-term effects within the paediatric population.

(v) 'Step down' units

Another particular issue in neonatal intensive care within the UK, is that with increasing centralisation of services, many babies requiring intensive care will be transferred back to a hospital closer to the parents' home during their in-patient stay. If the intervention continues to be administered, the process of approval, within these "step down" units is complex. The CTIMP will need to be transferred with the baby, often at short notice, to one of a large number of neonatal unit within the country. Issues to do with the identification of a principal investigator at every neonatal unit in the country, GCP training of all the neonatal staff in every neonatal unit in the country and monitoring every site within the country, for what may be a relatively modest size neonatal trial, are unnecessarily burdensome and will not protect the safety of the trial participants.

However, if a baby is transferred to a "step down" unit which does not have the necessary approvals, and the trial is stopped as a consequence of lack of approvals, then there will be substantial non-compliance with protocol, which will invalidate the results of the trial. Clarification within the Clinical Trials Directive about transfer of trial participants and their medicines, which limit the bureaucratic burden, would be helpful.

2) What impact has the CTD had on conducting trials in paediatric populations?

The ICREL report assessed the impact of the CTD generally but did not focus specifically on paediatric trials. There is a perception that paediatric trials are particularly difficult, and there is limited understanding and implementation of risk-based approaches. Sponsor insurance policies may also exclude trials in children entirely rather than being related to the level of risk involved. For these reasons, and given the new paediatric legislation, we believe it is important to gather similar information as presented in the ICREL report for paediatric studies specifically.

3) For clinical trial regulation, what options could be considered in order to promote the clinical research for paediatric medicines, while safeguarding the safety of the clinical trial participants?

Adequate involvement of appropriate paediatric specialists with good understanding of the CTD at all design and review stages. Figure 29 of the ICREL report suggests only half of EU Ethics Committees have competence in assessing paediatric therapeutic trials.

4) Would measures ensuring the transparency of clinical trials (e.g. access to information on EudraCT) to avoid unnecessary duplication and the creation of national and European networks (EU network of networks charged with implementing multi-national studies will need to address the issues of different interpretation between countries. This should help as should performance monitoring and education/training arranged centrally) of investigators and centres with specific expertise in paediatric studies ameliorate these issues?

Information by itself is not the whole solution. Networks should improve consistency of approach (design as one example) and encourage collaboration. Interaction required is between regulator, sponsor and investigator/network. This may be facilitated by the FP7 network of excellence.

5) Have you other suggestions as to how these issues could be addressed?

Interaction with regulators about which regulatory issues are paediatric-specific as opposed to generic ones. Greater dissemination from regulators re risk-based approach to inspections. Interaction required is between regulator, sponsor and investigator/network. This may be facilitated by the FP7 network of excellence.

Comments on generic issues within CTD

Issue summary	MCRN response
Issue 1: Multiple and divergent assessments of clinical trials - Increased administration costs - Assessment for parts of trials may not be in country with best expertise - Delays starting trials due to waiting for approval from each country - Inefficient resource use for NCAs	We would support a move to a single ethical review across multiple Member States if this included the proviso that the ethical review should take place in the country in which the sponsor is based. If this were not the case, we would oppose a move for a single ethical review across multiple Member States, however would support the establishment of a EU-wide network of ethics committees.
Issue 2: Inconsistent implementation of the CTD across EU member states 1. The aim of the CTD at European level was to achieve harmonisation – that this has had limited effect is attributed to 'inconsistent application'. The current situation gives rise to risks of insufficient patient protection and increased administrative costs. Four examples are given: a. Substantial amendments – about 21 000 reported to NCAs per annum. EC considers many are reported to avoid risk of non-compliance rather than because they are substantial	1. We support a formalisation of the Voluntary Harmonisation Procedure in law as well as robust national procedures. This may help in situations where regulators require study designs which are not feasible in UK (and if the FDA is involved may not be feasible in Europe). It may also be that investigators design studies that are not feasible because of the way in which an individual European country interprets the CTD e.g. UK considering that extemporaneous preparation is Clinical Trial manufacturing. So improved consistency in interpretation is required, perhaps by more careful/specific drafting to allow less local interpretation. On the specific examples listed: a. We support clarification of what a 'substantial amendment' is. b. We support greater clarity regarding the rules on SUSAR reporting, and removal of obligation on sponsors to reports SUSARs to Ethics Committees. We would not wish a single reporting system be accepted

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b. SUSARs – wide variation in reporting in Member States. Possible over and multiple-reporting c. Scope of CTD – differing interpretation of 'non-interventional'. In non-interventional trials, no additional diagnostic or monitoring procedures are applied and epidemiological methods are used for the analysis of data. The borderline between interventional and non-interventional trials is different in the different Member States, thus a trial can be considered non-interventional in one state and interventional in another State d. There is a particular UK issue because MHRA interprets 'extemporaneous preparation' of medicines in a pharmacy as manufacture which requires a CT manufacturing licence and QP release. Industry is increasingly interested in the use of 'industry verified' preparations of this type which might be acceptable to EMEA but would require CT licences if prepared in UK but not in many other EU countries. There is also confusion about what aseptic pharmacy preparation units can do without a CT licence and a feeling that there is no consistent approach across EU.	until full functionality of the Eudravigilance database has been demonstrated. c. We support clarification of the definitions of interventional/non-interventional trials. d. There is a practical problem if the UK interpretation is extended to all countries. We are happy with the MHRA interpretation at present because without validation of the method of preparation we would have no control over quality of extemporaneously prepared clinical trial materials. However, industry verification of the process would give appropriate assurance and, if allowed, might speed up the conduct of trials in children and make the process of paediatric drug development quicker and cheaper. We would like to see an exception to the UK interpretation which would allow extemporaneous preparation of industry verified preparations approved in a PIP without the requirement for the pharmacy to hold a CT manufacturing licence and without QP release of products.
Issue 3: Regulatory Framework not adapted to practical requirements The CTD is: 1. Not risk-commensurate: risks of trial relate to	1. We support a risk-based approach. We support a risk-based approach to regulation of academic trials. We oppose the complete exclusion of academic/non-commercial trials from the scope of the CTD as we feel that true harmonisation across Europe will not be achieved if such trials are excluded. We support the ability of an inspectorate to inspect against the full range of systems permitted by the flexibility intended in the Clinical

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actual circumstances of trial including nature of IMP and patient population. Risks for trial participants vary widely, but CTD is a one-size fits all approach. For example, one MCRN trial is undertaking a randomised controlled trial of oxygen saturation targeting in preterm babies who require ventilation and supplemental oxygen. The aim of the trial is to determine whether, within widely used and acceptable oxygen saturations limits, it is better to target saturations within the upper end of this range or the lower end of this range. Such a trial, in our view, is extremely low risk. We are merely formalising the clinical care processes used for ventilating preterm babies. And yet the systems in place are as burdensome as though it was a trial of a new agent being used for the first time in a vulnerable group. 2. Not adapted to practical circumstances, for example: (a) Requirement for a single sponsor for multi-country trials can cause problems, particularly for academic sponsors. Some sponsors are unable/unwilling to act as sole sponsor. We have also had one experience where the opposite was true. For one international trial, funded by the MRC, a University was acting as sponsor for this trial despite it being a multi-country trial.	Trial and GCP Directives. This would include a risk-based approach to clinical trial monitoring, including but not limited to on-site monitoring. We would urge that this is genuinely based on risk, with the level of monitoring appropriate for the actual risk, rather than perceived risk.. For example, in a trial of an accepted standard treatment being used with children or neonates, the level of risk should be considered low based on the use of a standard treatment rather than high based on the fact that the trial involves children/neonates. 2. (a) We support an amendment to the CTD to allow a sponsor in each Member State. (b) We support clarification of the training requirements in relation to the individual's role in the clinical trial.

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When researchers from Member State X were keen to participate in this trial, we were unable to proceed because the competent authority in that MS insisted that there was joint sponsorship between the UK and that MS. The University sponsor's interpretation of the Clinical Trial Directive was that there had to be a single sponsor and they could not accept co-sponsorship under these terms. One specific issue which may contribute to this situation is that if the sponsor is in one country, particularly if they are also providing insurance for the trial, as the particular university does, then if there is legal action against the sponsor, the process is conducted according to the law of the member state where the sponsor is. In this case, English law. In addition, with the same trial, the trial group was approached by centres in Member State Y, who were very keen to recruit and a lead investigator there had agreement from almost every large neonatal unit in that MS to participate. However, the authorities in that MS insisted that each individual clinician recruiting patients to the trial had specific insurance for the purposes of the trial with a company based in that MS. Once again, the university sponsor provided generous trial indemnity but this was with a company not based in MS Y, and despite	

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negotiations between the university sponsor and the MS authorities, this became an unresolvable issue and so, despite months of work, MS Y was not able to participate in this multinational trial. As a consequence of these problems, it was decided to recruit additional trial centres outside Europe, and Argentina was delivered a large number of suitable babies (480) to a high standard. (b) perceived need for GCP training for all staff with any role in trial and difficulties encountered in highly staffed areas such as A&E departments, PICUs, NICUs, shared care oncology sites.	