Running an international paediatric non-commercial clinical trial

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ABSTRACT

The current regulations for conducting non-commercial clinical trials in Europe are many and complex. These are explored from the perspective of a UK based non-commercial international clinical trial. The reasons for the difficulties encountered are discussed and suggestions made as to how best to overcome them. Improvements are suggested for our law makers and competent authorities. It is argued that the current regulatory environment could be considered unethical as it inhibits and delays research.

This paper is about the difficulties of conducting a non-commercial clinical trial in the current regulatory climate. Difficulties arise because of European and national regulations, often well intentioned. Non-commercial trials are common in paediatrics where rare diseases make up a large proportion of the workload and where both pragmatic and efficacy trials are required. Efficacy trials are designed to investigate whether or not a medicine has an important therapeutic effect. Pragmatic trials investigate whether medicines are effective in real life situations, that is, simulating general use where the patient or parent may decide the side effects are not worth the possible benefit, for example. Such issues only become apparent in pragmatic trials or, over time, by surveillance of the product in general use.

While we concentrate on the problems of conducting non-commercial pragmatic clinical trials in the UK, it is important to recognise that the benefits of standardised procedures across Europe could be considerable. If standards are raised as a result of the requirement to follow good clinical practice in relation to clinical trials, then the quality of research will improve. However, we believe the practical delays and costs outweigh the theoretical advantages of the new regulations: the risk benefit ratio is currently unfavourable. Ultimately, ECRIN, the European Clinical Research Infrastructure Network[1] may provide some necessary support for researchers but this is not yet available and will not solve many of the problems.

THE NEED FOR REGULATION

Commercial trials, that is, clinical trials run by the pharmaceutical industry, usually with the purpose of obtaining a marketing authorisation, have met with increasing criticism over the last few decades as it became clear that commercial interest had sometimes taken precedence over scientific rigour. The results of trials were not always made public and selective reporting of those that were published all contributed to the available information frequently being biased. As a result, more rigorous standards were created on how trials are conducted and reported. Particular improvement was made following: (i) the recommendations from the International Conference on Harmonisation of Good Clinical Practice in relation to clinical trials in 1996[2]; (ii) the CONSORT agreement on how results should be published[3 4]; and (iii) the registration of clinical trials.[5] European legislation has put much of this on a legal footing. In the UK, additional regulation of research has added to the problems.

THE EUROPEAN DIRECTIVE

These issues were debated at the European Parliament resulting in European Directive 2001/20/EC.[6] Directives within the European Union (EU) require each member state to introduce a law to comply with the directive but leave it to each country to decide how best to integrate this new law into their own legal framework. A major problem is that each country has incorporated this directive into their law in different ways, resulting in similar but different requirements in each member state. Additionally, very few countries have translated their laws into other languages, while some of those that have, have made this translation "unofficial". Thus each company or non-commercial research group is left to try and translate regulations at their own cost, duplicating effort, wasting time and potentially having different translations. Similar laws are being passed in other parts of the world too, again without consistency. While primarily directed at commercial trials, where corporate interests may prevail, these laws may also, as in Europe, apply to non-commercial trials.

THE BENEFITS OF NON-COMMERCIAL TRIALS

Non-commercial trials are independent of the pharmaceutical sector. They are required for rare diseases and to study drugs that have been available for many years. The UK childhood leukaemia (UKALL) trials are an example of such trials and have successfully transformed the outlook for children with leukaemia.[7] Such trials were undertaken before the current legal and regulatory framework and have contributed enormously, at low cost and low risk, to the improved health of children. Serious problems, such as fraud and fabrication, have been rare in non-commercial trials where there is little to be gained by such malpractice and where the scientific interest is to improve the outcome for patients. Such problems,

if they do occur, can often be detected by careful central data monitoring.[8]

THE EFFECT OF THE EUROPEAN DIRECTIVE ON NON-COMMERCIAL TRIALS

Since the introduction of the EU directive into member state law, non-commercial trials have been subject to the same rigorous standards as commercial trials. This requirement happened at a very late stage in the planning process. Unfortunately, little practical discussion took place about the effect that this would have on non-commercial trials. Pharmaceutical industries can fund clinical trial activity and reclaim the cost of trials by charging for new pharmaceutical products. In comparison, non-commercial trials have to raise funds from more limited sources.

The new clinical trial regulations will, in our view, have a severely deleterious effect on non-commercial research due to the increased cost (box 1). This is despite new European funding streams and the financial incentive for commercial companies for studies that will lead to an extension to the licence.[9] With a limited amount of funding for non-commercial trials available, the effect of the new regulations will be that fewer trials are undertaken. If this happens then the current regulations could be viewed as unethical.

SPONSOR

All clinical trials require a sponsor. This is a legal term for the person or organisation ultimately responsible for running the clinical trial. Sanctions against the sponsor can now include imprisonment – perhaps necessary for extreme malpractice in the commercial sector but inappropriate for the non-commercial sector. In the UK, within the NHS, the development of a non-commercial clinical trial agreement (now called mNCA; model non-commercial agreement) has only just been published after over 4 year's gestation.[10] It is possible for an NHS trust (hospital or primary care provider) to be the sponsor for an international trial and the NHS Litigation Authority for England will underwrite the financial responsibility for negligent liability held by the sponsoring trust in relation to the protocol. This responsibility has to be borne within the research governance framework (2005)[11] that provides that the protocol will be properly peer reviewed. Clinical negligence for patients at each NHS site will be covered by the clinical negligence scheme for the trust, provided research and development (R&D) approval has been obtained (see below).

Box 1 Major problems that will be encountered

- A rapidly changing regulatory environment
- Different interpretation of the EU clinical trials directive in different European countries
- Lack of clarity over the number of sponsors within Europe and elsewhere
- The requirement that medicines must be free to those taking part in clinical trials adds to costs and may be considered an inducement where medicines normally have to be paid for
- Charges (initial and for amendments) levied by some ethics committees and competent authorities
- Lack of official translations of documents within Europe
- Requirements (for amendments) that are too onerous
- A bureaucratic approvals process in the UK that takes time and that can lead to a refusal to undertake a trial at some sites
- Insurance and indemnity vary within Europe
- The requirements of tracking, accountability and labelling that may need to be reduced through use of "specific modalities"

Sponsoring international multicentre trials

There is a lack of clarity about the number of sponsors that are required. There should be one sponsor with overall responsibility for the trial so that the protocol cannot be altered or adjusted by others. The laws of each member state, however, often require a sponsor within each member state. For example, Germany can accept a UK sponsor but Italy cannot. This has come about in order to be able to hold a person or body responsible within each country's legal system. But, since the scientific integrity of a trial needs to be maintained across the countries in which the trial is undertaken, this arrangement of having separate sponsors could, potentially, allow each sponsor to adjust the protocol or to have different monitoring. In the UK, the MHRA, the competent authority for approving and inspecting clinical trials, is only interested in inspecting what is taking place in the UK, thereby ignoring what is taking place outside the UK. Deviations between protocols in separate countries are not therefore likely to be detected. Neither are they likely to be picked up by the sponsor (where there are many) or the publisher (after the event).

ETHICS AND HOSPITAL MANAGEMENT APPROVAL

In the UK it is possible to get multi-centre research ethics approval. In Europe, each country (and sometimes each local area) will require their own ethics approval and the arrangements and requirements for ethics committee review in each country are very varied.[12] In Germany you need national, local and regional approval. All these bodies may raise questions and make suggestions for changes to protocol, information sheets, etc, making it difficult and expensive for the management of the trial. This process is not making a trial more ethical. The cost in time and money for this multiple review process is in itself unethical and needs to be addressed by the politicians at national and European level.

Research ethics committees in the UK have indicated that they do not always have the necessary experts on their committee to approve the science of an application. For this reason peer review now has to be obtained through the R&D approval process if it has not already been done. Some local R&D departments are each undertaking their own peer review before giving R&D approval, even when this has already been obtained by the sponsor or funding agencies. We advise keeping a note of all peer review, even that occurring through discussion at meetings or through development of the protocol, as this, along with the final peer review of the final protocol, helps to defend the trialists from accusations of negligence. It can also be provided to local R&D departments as evidence of adequate peer review.

In the UK it is necessary to obtain local approvals from each hospital where the trial will be undertaken and this has led to extreme delays. This is usually done by the local R&D department. Attempts are being made to improve this system with the introduction of a central sign-off system for research.[13] However, it remains to be seen if this will lead to improvement or be accepted by all hospitals. A similar attempt to introduce "research passports" to avoid each hospital issuing an honorary contract to researchers from other hospitals has not yet been successful because of local resistance.

We advise, since an annual report is required by the ethics committees and in the UK by R&D departments, that you only have one date on which this is produced and submit the same report to each national committee at the same time. If you have already produced an annual report covering countries already taking part, submit this with your ethics and regulatory applications to new countries and ask that the date of your annual report be aligned to the date already in place for your trial.

COST OF DRUGS

The regulations now require that drugs are provided to a patient in a clinical trial free of charge. This is appropriate for commercial trials of new medicines. It is inappropriate for non-commercial trials investigating an existing treatment. In the UK, children will obtain their prescription free, but this is not the case across the EU. The trial then has to bear the cost where prescriptions are not free. In contrast to the situation for a commercial trial, this requirement could be considered to be acting as an inducement for the patient to take part in the trial since, if they do take part, they will get their treatment free. Such inducements are unethical and this therefore needs urgent review by the European Parliament (box 2).

INSURANCE AND INDEMNITY

In the UK, obtaining approval to undertake non-commercial research in an NHS trust brings with it automatic indemnity insurance for negligent harm. The system for obtaining local hospital approval varies from country to country and, as in the UK, is often intertwined with obtaining insurance indemnity for a non-commercial trial. Commercial trials run by the pharmaceutical industry have to follow strict guidelines throughout Europe in the provision of compensation. For commercial trials, this usually includes no fault compensation. In the UK it is illegal to provide no fault compensation for people taking part in an NHS sponsored trial. In Switzerland, no fault compensation is a legal requirement for all trials including non-commercial trials. Although not part of the EU, Switzerland does follow many of the directives from the EU and has incorporated good clinical practice in relation to clinical trials into Swiss law.

Box 2 Issues requiring the urgent attention of the appropriate responsible bodies

- A uniform nomenclature for investigators throughout Europe
- Official translations into other languages of the regulations within each country
- Provision for a sponsor responsible for the protocol internationally while having subservient country (or sub-country) sponsors responsible for local issues but not for the protocol
- A single ethics approval system for Europe
- A single competent body approval for trials within Europe – presumably the EMEA
- A central R&D approval process for each country
- The requirement for investigational medicinal products (IMPs) to be free to the participant needs to be changed
- A clear system for effective *independent* monitoring of all adverse reactions within a trial combined with removal of the need to report adverse reactions to other bodies
- Removing the addition of sites as a substantial amendment to a clinical trial authorisation or ethics committee
- An adjustment to the standards to which trials are inspected – in relation to the risk benefit ratio. Non-commercial trials should not be regulated or inspected to the same standard as commercial trials
- A requirement that no charge is made for ethics and other approvals, and amendments, for non-commercial trials
- A clear statement making it unnecessary to undertake labelling and tracking of IMPs where they are already in use, without the requirement that they are used on patients with the same characteristics as those covered by the authorised indications

CLINICAL TRIAL AUTHORISATION (COMPETENT AUTHORITY APPROVAL)

Clinical trial authorisation is required in each member state where a trial is being undertaken. An investigator's brochure giving details for doctors participating in the trial, with all necessary information about the pharmaceutical product is required. If a medicine is licensed, one can use the summary of product characteristics (SpCs; the patient information leaflet) as the investigator's brochure. This may be the simplest way for a non-commercial trial to produce an investigator's brochure for a trial only taking place in one country. But, for multinational trials, this either leads to a different investigator's brochure in each country for the same trial (because the marketing authorisation in each country frequently has different information for the same product within each member state even when the pharmaceutical product is provided by the same company) or gives advice different to that which the medical practitioner is used to. This should change with the introduction of new pharmaceutical agents, but may continue to exist for a long time for products that already have a marketing authorisation. The latter are the products that are likely to be subject to investigation by non-commercial trials. It may therefore be better for international non-commercial trials to produce their own investigator's brochure.

Other inconsistencies also exist, for example with marketing authorisations that specify the treatment of a particular disorder which occurs in an age group for which the marketing authorisation does not give approval. These need to be dealt with in any application and are therefore best discussed in the protocol (or the prequel to a protocol – see below). In addition, different charges are applied by the competent authority in each country so that a charge may or may not be made when the competent authority approves a non-commercial trial. Since this additional approval is not adding to patient safety or improving science, the regulations need to be changed to allow one competent authority to approve a trial within the whole EU, with one sponsor, while notifying each competent authority of the sites where the trial is being undertaken in that state for patient safety and inspection purposes.

Amendments to the clinical trial authorisation are burdensome and expensive, with a cost of up to €4000. In the UK, the definition of a substantial amendment (one that has to be notified to the MHRA), includes, for example, the addition of a new site. This cannot be a significant risk to the trial participants if local approvals and normal trial controls are in place – so, why is this designated a substantial amendment? The financial cost and time spent increase the difficulties for those running a clinical trial and therefore indirectly decrease patient safety.

National requirements change and it is difficult for non-commercial trials to keep up with such changes. Germany has

two competent authorities. Different definitions of an investigational medicinal product (IMP – the medicine being evaluated) also add to the difficulties between member states as do different names for personnel. In Germany, the senior national investigator is called the chief investigator (even in an international trial), while in the UK the chief investigator is the senior investigator for the whole international group of investigators.

We advise that one method of reducing these difficulties is to have a prequel to the protocol that is specific to each country and that deals with local country specific issues without changing the science of the trial. This can also document indemnity and other local issues. Changes to this document would not be changes to the protocol and would not require reporting to each country – only to the one to which the prequel relates.

ACCOUNTABILITY (LABELLING, TRACKING AND COMPLIANCE)

The accountability of IMPs is a key requirement and is understandable for an IMP produced specifically for a trial where the IMP (or a placebo) will need to be stored safely and where they cannot be used outside the trial. This ensures every dose is accounted for and disposed of or returned to the sponsor after the trial, if supplies remain. The cost of accountability is very high, yet it is of little or no value to many non-commercial trials. The European Commission has produced draft guidance on specific modalities for non-commercial clinical trials.[14] It allows the competent authority to agree to the absence of specific labelling and minimal tracking, that is, a knowledge of who received which drug with an evaluation of compliance.

Although the MHRA in the UK have been helpful in using specific modalities to reduce the burden on researchers, it is not yet clear to what extent other European countries will follow. UK hospital pharmacies that have already been inspected by the MHRA often find it difficult to believe that these specific modalities will be acceptable; this frequently leads to a delay in obtaining local R&D approvals.

SAFETY REPORTING

The regulations require notification for serious adverse events (SAEs), serious adverse reactions (SARs) and suspected unexpected SARs (SUSARs). Different member states have different regulations, some requiring all sites and ethics committees to be told of SARs, usually without making it clear whether this can wait for the annual safety report. But, who is acting on this information and with what competence and authority? At present, each member state's competent authority wishes to know of all SARs wherever they occur – requiring multiple reporting when we already have the EMEA who should coordinate this. It is then very difficult to know how many individual SARs have actually occurred. In the UK, ethics committees do not appear to know what to do with information on SARs when it is given to them (as required) or what their role is in relation to this information since they do not have the resources, and may not have the expertise, to deal with this. SARs occurring outside the EU also have to be reported to the competent authorities within the EU. It would be easy to conclude that there is no effective oversight of safety under the current regulations within the EU other than by the sponsor – exactly the situation the regulations were supposed to avoid. Data protection regulations only add to the difficulties by making it almost impossible to eliminate duplicate reporting.

Box 3 Recommendations

- Read the regulations – do not believe everything you may be taught on a good clinical practice course.
- Do not say you will do anything that is not required unless you have a very good reason.
- Where possible use guidance and not regulations for your own operating procedures.
- Rigorously track changes to your documents while they are in preparation – especially your protocol.
- Appoint users (parents or children) early enough to help you develop the protocol and information sheets. Ask their opinion about outcome measures.
- Document every detail of peer review. Prepare someone to do your final peer review on time.
- Align your annual reports to the annual data lock point for your own competent authority. Insist on using this date for all reports to all bodies (ethics, safety and site reports) in all countries.
- Have your own investigator's brochure and do not use summary of product characteristics (SpCs) if your trial is international.
- Have a prequel to your protocol specific for each country. Read the EFCGP publication on ethics approval in the EU.[12]
- Consider central monitoring for fraud and misconduct.
- Minimise all information you require investigators to return to you.
- Appoint your data monitoring and ethics committee well before you intend to start recruiting.
- Develop your case report forms (CRFs) to be as easy to use as possible. Make sure you have systems for checking data as it comes in.

The first approval from a competent authority will give you your "data lock point" (information available up to that date is included) for your annual safety report. Each year all information available up to this point must be incorporated into your safety report and sent to the competent authority within 60 days. We advise that you insist on using this date for all safety reports worldwide and you will save a lot of time. To achieve this, make it part of your application. You have to review all information on your IMPs for this report, so check on that date that the marketing authorisation(s) (SpCs) have not changed. Check a database of publications to make sure no new research will impact on the safety of your trial. Try to persuade those countries that request more frequent reports to accept an annual report (unless this is not appropriate because of the large numbers of patients being recruited – unlikely in a paediatric non-commercial trial).

ADVICE FOR CHIEF INVESTIGATORS

First of all, read the regulations and understand them. Those in the UK should visit the Medical Research Council's website[15] to access their advice. Our advice is summarised in box 3. Make sure supplies will be easily available and if you are manufacturing even a placebo, prepare for labelling and to undertake tracking. Consider how you will document that the correct prescription has been written – do you need a form for this? Most important of all, look again at your protocol and these procedures together and make sure they are compatible and as simple as they can be. Can you confirm that the patient exists (to prevent fraud) in some way without a site visit – perhaps by

setting up a notification scheme through a third party within the hospital/trust such as the laboratory if a laboratory test confirms the diagnosis for you? Look at potential costs of your trial and evaluate how they can be minimised and paid for. Find a sponsor – for a UK NHS employee this should be your hospital.

Make sure no site begins recruiting until all approvals are in place – ethics, R&D and competent authority approval with insurance where needed. You will need a contract between your sponsor and each site. Don't forget, especially if you have an R&D department that is less active than you would like, that the sponsor can delegate some of these responsibilities (but they retain the liabilities). Think of your processes for managing SARs and for chasing and managing outcome information. Which data are so important that you will make every effort to obtain them and which are less important. Consider data protection regulations carefully, make sure that you only request information that you must have – this also helps your hard pressed principal investigators at each site – and make sure you have informed consent for information that must leave your trust. Anonymise the information wherever possible and use pseudo-anonymisation (coded information) everywhere else that you can. Finally, ask your R&D department or other employer to undertake a risk assessment – this may help you to reduce the problems that you will encounter.

CONCLUSION

The more stringent the regulations become, the fewer trials will be done and the less science will be available for clinicians wishing to treat their childhood patients in the best way possible and for parents wishing to know more about their child's treatment. In this way, the current regulations are seriously inhibiting new research and can be considered unethical.[16] The financial benefits that pharmaceutical companies obtain for extending their investigations into the paediatric age group will not improve the outlook for the majority of non-commercial trials.[9] We urge the Paediatric Committee at EMEA to help streamline the process for multinational paediatric clinical trials.

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