

RUNNING AN INTERNATIONAL PAEDIATRIC NON COMMERCIAL CLINICAL TRIAL

Professor John P. Osborne

Consultant Paediatrician, Royal United Hospital, Bath and

Honorary Professor of Paediatrics and Child Health, The School for Health,

University of Bath.

Dr Stuart Edwards, Trial Manager and Research Co-ordinator, The School for

Health, University of Bath.

Dr Finbar J. K. O'Callaghan, Consultant Senior Lecturer, Faculty of Medicine and

Dentistry, The University of Bristol.

Key words

Clinical trials; Research Governance; Good Clinical Practice (GCP); Research

Ethics; European Clinical Trials Directive

SUMMARY

The current regulations for conducting non commercial clinical trials in Europe are 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 these. Improvements are suggested for our law makers. It is argued that the current regulatory environment could be considered unethical as it inhibits research.

INTRODUCTION

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 regulation. The requirements are constantly changing, including attempts to reduce the difficulties that have been introduced. As trials often run over a number of years, any change over that period can introduce new challenges. We attempt to highlight the problems we have faced and to give hints on how to manage some of the problems. We also highlight some things we believe should change. Non commercial trials are common in childhood disorders where rare diseases make up a large proportion of the workload and where pragmatic trials are of more value than efficacy trials. Efficacy trials are those that concentrate on showing whether or not a medicine has an important therapeutic effect. Pragmatic trials are those that concentrate on the benefit of medicines in real life situations. Not all medicines shown to be efficacious are used in practice, usually because for some reason they are not suited to the majority of patients.

THE NEED FOR REGULATION

Commercial trials, ie 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 precedent 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 the introduction of the recommendations from the International Conference on Harmonisation of Good Clinical Practice (GCP) in relation to clinical trials in 1996¹, with the CONSORT agreement on how results should be published² and with the registration of clinical trials³. In the UK there is also an NHS clinical trials register⁴. However, despite the progress made by the pharmaceutical industry, there was still a belief that legislation needed to be introduced in order to make sure that all companies were compliant and that information from trials was readily made available in the public interest. This should include data from sites outside Europe where trials have sites both inside and outside Europe.

THE EUROPEAN DIRECTIVE

These issues were debated at the European Parliament resulting in European Directive 2001/20/EC⁵. Although this directive was initially conceived as applying to commercial trials, non-commercial trials were included. Directives within the European Union require each member state to introduce a law to comply with the directive but leaving it to each country to decide how best to integrate this new law into their own legal framework.

Member states had until the spring of 2005 to comply with this directive. Many were late in doing so – some very late. However, 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. To add to this difficulty, very few countries have translated their laws into other languages and 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 an inaccurate translation (depending on the quality of translator and

the translating process). Similar laws are being passed in other parts of the world too, again without consistency and while primarily directed at commercial trials, where corporate interests may prevail, as in Europe, they may also apply to non commercial trials.

THE BENEFITS OF NON COMMERCIAL TRIALS

Non commercial trials clearly include those that are independent of the pharmaceutical sector. The degree of independence from the pharmaceutical sector varies from no involvement to provision of medicines or placebos to even funding the trial but in such a way that the pharmaceutical company cannot influence the conduct or reporting of the trial. Many such trials have been undertaken in the past and perhaps some of the best known, not just in the UK, are the UK childhood leukaemia (UKALL) trials. Over the last 40 years these trials have successfully transformed the outlook for children with leukaemia where nearly all children with acute lymphoblastic leukaemia used to die, now they have an 80% chance of survival⁶. Such trials were undertaken before the current legal and regulatory framework and have contributed enormously to the improved health of children.

Although not unheard of, serious problems, such as fraud and fabrication have been very 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. In fact the effect of fraud and fabrication is not as great as might be expected, and can often be detected anyway by careful central data monitoring⁷.

THE EFFECT ON NON COMMERCIAL TRIALS OF THE EUROPEAN DIRECTIVE

So, where are we now? 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. The European Parliamentarians decided that if the directive was good for the science of the pharmaceutical industry, why was it not also good for the science of non commercial trials? Unfortunately virtually no practical discussion and no meaningful dialogue took place about the effect this would have on non commercial trials.

Pharmaceutical industries are very well financed for their clinical trial activity, although the cost of trials undertaken in order to obtain a marketing authorisation is one of the reasons for the high cost of new pharmaceutical products. In comparison, non commercial trials have in the past often been successfully run on a financial shoe-string.

There is an enormous lack of information available about the use of pharmaceutical agents within the childhood population where off licence use is almost the norm, because of the lack of commercial value in obtaining a marketing authorisation for the childhood population. The new regulations will, in our view, have a severely deleterious affect on research into the value of many pharmaceutical products, particularly older medicines and for those “uncommon” diseases, due to the massive increase in bureaucracy and the resultant cost. It should be remembered that there are so many uncommon diseases affecting children that together they affect as many children as common conditions. With a limited amount of funding for non commercial trials, fewer trials are likely to be undertaken and this suggests that the current regulations could be viewed as unethical. But, what are the main effects of the regulations so far, how are they impacting on current attempts to run clinical trials and what can be done to limit the problems that have been created?

SPONSOR

All clinical trials now 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 include imprisonment – perhaps necessary to inhibit extreme malpractice in the commercial sector but hardly encouraging for the non commercial sector. Non commercial trials cannot afford to set up paper companies to take this responsibility as commercial companies can. The new directive makes it clear that a commercial pharmaceutical company can delegate activity to a CRO (commercial research organisation) but the pharmaceutical company still retains the ultimate responsibility for what happens during the trial. However, non commercial trials have in the past often operated with a loose arrangement of clinicians willing to undertake clinical trials for the benefit of their patients. Responsibility was often shared but now has to be held by one organisation, requiring a new layer of bureaucracy. Within the NHS, the development of a non commercial clinical trial agreement (now called mNCA; model non-commercial agreement) is still in it's draft form after over 3 years gestation! For a long time it was unclear if an NHS organisation could undertake the role of a sponsor for an international trial (even perhaps for one running in all 4 countries in the UK where separate Departments of Health and therefore separate litigation arrangements exist). This has now been clarified so that at least in England it is possible for an NHS Trust 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)⁸ that provides that the protocol will be properly peer reviewed. The risk in relation to the protocol would then be very small. Within the NHS, clinical negligence for patients at each NHS site will still be covered by the clinical

negligence scheme for the trust. In effect however the NHS Litigation Authority picks up the bill so the cost is spread across all trusts if any claim occurs. Litigation arrangements may now differ in Foundation trusts if they opt out of the NHS litigation scheme – at present an unlikely scenario but one that may impact on clinical trials in the future.

SPONSORING INTERNATIONAL MULTICENTRE TRIALS

There is a lack of clarity about the number of sponsors that are required. Whilst it is clear from the regulations that there needs to be **one** sponsor with overall responsibility for the trial so that the protocol cannot be altered or adjusted by others, it is also clear that the regulations incorporated into the law of each member state often require a sponsor within each member state. For example, Germany can accept a UK sponsor but Italy cannot. The situation gets even more complicated for a trial that goes outside Europe with a sponsor required independently in Australia and New Zealand for example. 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, for example, to adjust the protocol or to have different monitoring. This would lead to uneven and therefore potentially dangerous science and leads again to increased bureaucracy. It also leads to the situation where the MHRA, the UK's 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 publisher.

ETHICAL APPROVAL

In the UK it is possible to get Multi-Centre Research Ethics approval. It has also been necessary to get local site specific approval but the NHS is changing this so that local site specific ethics approval will soon not be required. But most of the activities undertaken and checked within this approval have now been passed to Research and Development (R&D) departments at each site. These sites are currently autonomous within each trust at each NHS site and although each site should be following the Research Governance Framework (2005), there has as yet been no effective central guidance for R&D departments, such as that given to the Research Ethics Committees. Thus there has been a proliferation of different levels of vetting prior to local approval (see below) that has at present increased the difficulties in obtaining approval to conduct clinical trials. This has been made worse because of the fear of inspection by the MHRA – those departments that have been inspected often request standards that are not necessarily required (see below) but which have been expected during the inspection.

At the same time, the 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 R&D departments are undertaking their own peer review before giving R & D approval, even when this has already been done by the sponsor. Thus, it is very important that protocols are properly and systematically peer reviewed and that this review includes all essential documents. These documents need to be rigorously tracked for changes, so that it is clear that the final documents are those that have been approved. We advise you to keep 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 finalised protocol, helps to defend the trialists from accusations of negligence.

In Europe, the situation gets even more complicated since each country will require their own ethical approval and the arrangements and requirements for ethical committee review in each country are very varied. The current situation has been helpfully summarised in a special edition of the International Journal for Pharmaceutical Medicine through the European Forum for Good Clinical Practice Ethics Working Party⁹. In some countries not only do you need national approval and local approval but there is an intermediate layer of regional approval (Germany for example). All these bodies potentially might throw up minor queries and questions and suggestions for changes to protocol, information sheets etc, making it extremely difficult and expensive for the management of the trial. It is very unlikely that this process is making a trial more ethical – it is more likely that it is merely the effect of different opinions and standards across countries. 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.

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 ethical application 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 makes perfect sense for a commercial trial where the patient is doing the company a favour by trying out a new treatment that may be of financial benefit to the company. It makes no sense for non commercial trials investigating a treatment or treatments that have been around for a long time. In such circumstances the patient is going to be treated, possibly with the same medication, but outside a trial if not within and the trial may be finding out perhaps the best dose, duration, type or combination of treatment. In the UK children will at least obtain their prescription free but this is not the case across the European Union. 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 a bribe for the patient to take part in the trial since if they do so they get their treatment free. A bribe is unethical and this therefore needs urgent review by the European Parliament. This situation is a good example of the conflict that arises when a law that was primarily designed for commercial trials has, at the last moment, been applied to non commercial trials.

HOSPITAL/MANAGEMENT (R&D) APPROVAL AND INSURANCE/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 United Kingdom it is illegal for an NHS trust 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.

Most hospital approvals, and all in the UK, will require an update ostensibly to see if the trial is going according to plan. However, some are now requesting three monthly reports and this is clearly not appropriate for many paediatric trials on relatively uncommon conditions. We advise that if this applies to you, put in your protocol that you will only be producing annual reports – it will strengthen your ability to decline to produce more frequent reports that will clearly be a distraction and an unnecessary and costly administrative burden. Insist on producing one annual report on the same date for each department – and align this with the date of your annual safety and ethics reports.

Currently in the UK it is necessary to obtain local approvals from each trust where the trial will be undertaken. Attempts are being made to improve this system with the introduction of a central sign off system for research. However it remains to be seen if this will be accepted by the trusts – especially foundation trusts. A similar attempt to introduce “research passports” to make it unnecessary for each trust to issue an honorary contract to researchers from another organisation is not yet succeeding because trust’s HR depts have been unwilling to accept them.

CLINICAL TRIAL AUTHORISATION (COMPETENT AUTHORITY APPROVAL)

The European Directive requires that clinical trial authorisation is in place in each member state where a trial is being undertaken. The regulations for obtaining a clinical trial authorisation require the provision of an **investigators brochure**. This gives details, for the medical practitioners taking part in the trial, of all necessary information about the pharmaceutical product. It is possible to use the marketing authorisation, the Summary of Product characteristics or SpC) as the investigators brochure if a product has a

marketing authorisation. This may be the simplest way for a non-commercial trial to produce an investigators brochure for a trial only taking place in one country. But, for those taking part in multiple countries, this either leads to a different investigators 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 absurd state of affairs should die out within Europe with the introduction of new pharmaceutical agents but may continue to exist for a long time for products that already have a marketing authorisation. These are the very 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 investigators brochure. Other inconsistencies also exist, 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 and these need to be dealt with in any application and are therefore best discussed in the protocol. 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.

To add to the problems, amendments to the CTA are burdensome and expensive, with the cost varying from nil to 4000 Euros. The definition of a **substantial amendment** (one that has to be notified), includes for example the addition of a new site. This only

adds to the cost and can hardly be a significant risk to the trial participants if local approvals and normal trial controls are in place - so why does the European Medicines Evaluation Agency (EMA) designate this a substantial amendment? The financial cost of this and the distraction it provides increase the difficulties for those running a clinical trial probably as a result of decreasing patient safety. In addition, national requirements change and how are non-commercial trials to keep up with such change without continuous translation costs? One country even has two competent authorities and knowing which to go to has only recently been aided by a translation into English. Different definitions of an IMP also add to the difficulties between member states as do different names for personnel – in Germany the senior investigator within Germany is called a 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 dealing with some of 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.

ACCOUNTABILITY (TRACKING AND COMPLIANCE)

The accountability of investigational medicinal products (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 (so this must include making sure every dose is accounted for and returned to the sponsor after the trial, if supplies remain). But what is the need to provide separate supplies that can be tracked for an IMP that is already in the pharmacy for routine use? The same need to return the product does not apply to drugs that already have a marketing authorisation even if that marketing authorisation is for a different age group

or condition. The cost of accountability is very high yet it is of little or no value to many non-commercial trials.

Pragmatic trials have been very useful over the years in showing the value of medicines when used in practice as opposed to efficacy studies where only the effect on those who have taken the medicine is wanted. Pragmatic trials assume that difficulties will arise for example with storage (and compliance) in different ways for different medicines or preparations of the same medicines, and this is useful practical information on the real value of the medicine when later used for patients outside a trial. This pragmatism requires an absence of tracking. A good example is the lack of benefit from immunisations when they have not been stored at the correct temperature. Why have more rigorous standards for trial medicines than will apply when the product is marketed? Why not see how effective the medicine will be in practice? Although the MHRA in the UK have been helpful in requiring minimal tracking, it is not yet clear if other European countries will be so compliant and UK hospital pharmacies that have already been inspected by the MHRA often find it difficult to believe that minimal tracking will be acceptable when an inspector visits. The regulations on tracking are another good example of the lack of adequate thought given to the impact of these regulations on non-commercial trials.

In a commercial trial looking to obtain a marketing authorisation for the product, it is felt necessary to know whether the patients took the treatment and what effect it had - although the trial results *should* still be analysed on an intention to treat basis. In a pragmatic non-commercial trial, the patients may not take the treatments for a variety of reasons and this is partly why the treatment may not work as well as it does in a commercial trial. Taken to its logical conclusion however tracking should include compliance – knowing that the medicine has been taken by the subject. It is often then

assumed that the patient is actually taking the treatment. But, this can only be done by analysing blood or urine samples for example. Even counting tablet returns does not prove that a patient has taken the treatment.

LABELLING

Similar problems arise with labelling of an IMP. Where the product is not known through routine use, new and clear labelling of the IMP is essential, since no other labelling exists. In a pragmatic non-commercial trial where the aim is to see what effect the usual treatment has on a condition, there is no need for special labelling since the product is already marketed and labels (and information sheets) exist. The direct and indirect cost of labelling needs to be considered against the benefit and the clinical trials unit at the MHRA in the UK can be very helpful in using their discretion to provide exemption from labelling, where they consider it appropriate.

PLACEBO

Placebos are not always ethical in paediatric research – injecting a placebo would not be appropriate for instance. Sometimes the adverse effects of a drug will unmask the clinicians, making attempts to blind treatment ineffective. The regulations for manufacturing are burdensome and once you are manufacturing even a placebo, tracking and labelling become an issue – yet having a placebo or making two treatments indistinguishable (a particular problem in paediatric practice where different formulations may be needed for different aged children in the same trial) improve the quality of the science. This all needs to be made more cost effective to undertake.

SAFETY REPORTING

The regulations require a bewildering number of notifications 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 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. The current arrangement will undoubtedly lead to multiple reporting by each member states competent authority to the EMEA and it will be very difficult to know how many individual SARs have actually occurred. In addition, at least in the UK it is clear that ethics committees do not 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. The first approval from a competent authority will give you your data lock point for **annual safety reporting** – 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.

ADVICE FOR CHIEF INVESTIGATORS

First of all, read the regulations and understand them. Those in the UK should visit the medical research council's website¹⁰ to access the clinical trials toolkit. Then when you write your protocol, do not say that you will do anything more rigorous than the regulations require or you will be inspected to those higher standards. Similarly, be careful about your SOPs (standard operating procedures – your bible of how the trial will be run. Think carefully about your Investigator's brochure. If you are undertaking a national trial, consider using the SPCs but for an international trial it may be worth developing your own investigators brochure. Consider having a prequel to your protocol specific for each country. Make sure supplies will be easily available and if you are manufacturing even a placebo, prepare to undertake tracking. Consider how you will document that the correct prescription has been written – do you need a form for this? What labelling will you have? Best of all is to re-look at your protocol and these procedures together and make sure they are compatible and as simple as they can be. Consider central monitoring as your method of detecting fraud and fabrication as it is much cheaper than on-site monitoring. Can you confirm that the patient exists 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 Trust. Universities may be reluctant to sponsor paediatric trials, but some will.

Keep a track of all the different forms of peer review that your protocol has had and get one final review when everything is finalised – there is safety in this process for you. Decide who will be providing this peer review and have them ready to do this before you need them. Always 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 also 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. 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. Finally, don't lose your sense of humour – you will need it!

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 unethical¹¹. Improvements to the benefits that pharmaceutical companies obtain for extending their investigations into the paediatric age group, while beneficial, will not improve the outlook for the majority of non-commercial trials¹².

REFERENCES

1. www.ich.org. ICH stands for The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use.
2. Moher D, Schulz KF, Altman DG, CONSORT Group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001;357:1191-4. see also www.consort-statement.org
3. <http://isrctn.org> administered by Current Controlled Trials Ltd.
4. <http://www.nrr.nhs.uk/>
5. http://www.wctn.org.uk/downloads/EU_Directive/Directive.pdf
6. http://www.lrf.org.uk/media/images/ChildhoodALL_2154.pdf
7. Buyse M, George SL, Evans S et al. The role of biostatistics in the prevention, detection and treatment of fraud in clinical trials. *Statist. Med.* 1999, 18; 3435-3451.
8. Research governance framework for Health and Social Care, second edition 2005. Published by the Department of Health, UK.
9. The procedure for the ethical review of protocols for clinical research projects in the European Union. *International Journal of Pharmaceutical Medicine*, 2007, 21; Number 1, pages 1-113.
10. <http://www.mrc.ac.uk/PolicyGuidance/EthicsAndGovernance/ClinicalResearchGovernance/ClinicalTrialsToolkit/index.htm>
11. Iain Chalmers. Regulation of therapeutic research is compromising the interests of patients. *Int. J Pharm Med* 2007 ;21 :395-404.
12. Regulation of drugs for children in Europe. Choonara I, *BMJ* 2007;335:1221-2