NCRI PET Research Network response to Clinical Trials Directive 2001/20/EC

Introduction

At present PET trials in the UK and Europe are subject to the same regulatory guidelines as therapeutics, producing a disproportionately large obstacle for PET research in the UK. The NCRI PET Research Network (PRN) and the Medical Research Council (MRC) are in dialogue with the Medicines and Healthcare Products Regulatory Agency (MHRA) to try to improve the regulatory environment for PET research in the UK. However, the European Medicines Agency (EMEA) issues regulatory guidance throughout europe, which limits the scope of the regulatory authority in each individual country to modify regulations.

Clinical trials in Europe are subject to the Clinical Trials Directive (CTD), which aims to:

- Protect the health and safety of clinical trial participants
- Protect the ethical soundness of the clinical trial
- Protect the reliability and robustness of the data generated in clinical trials
- Simplify and harmonise the administrative provisions governing clinical trials in order to allow for cost-efficient clinical research

Whilst introduction of the CTD has brought about improvements in safety, ethics and the reliability of clinical trials data, it has also led to a decrease in the attractiveness of patient-orientated research in the EU since these have become more difficult and expensive to perform. EMEA has recently recognised that the current CTD guidelines may not be optimal for all clinical trials and is undertaking an assessment exercise to consider various options to further improve the functioning of the CTD. Some of the issues that hinder PET imaging trials clearly fall within the remit of several consultation questions, so there is an opportunity for the PRN (and individual PET researchers) to raise these concerns with EMEA and perhaps decrease regulatory barriers for academic PET trials at a European level. The relevant background information and consultation questions are shown below, followed by the proposed responses from the PRN.

Background to the NCRI PET Research Network

The NCRI PET research initiative aims to stimulate and support the build-up of a UK research programme in PET involving both clinic and translational research. Leadership is being provided by the PET Research Steering Committee and the PRN provides an interface with the scientific and medical communities and the NHS. The Network is providing intelligence on developments, needs, opportunities and barriers to research as well as acting as a catalyst for practical action. Further information is provided on the website (www.ncri-pet.org.uk).

Please note that this response reflects discussion and views of the NCRI PET Research Network; it does not necessarily reflect views of individual NCRI partners.

CTD ASSESSMENT EXERCISE, KEY ISSUE N°3 TO BE ADDRESSED: REGULATORY FRAMEWORK NOT ALWAYS ADAPTED TO THE PRACTICAL REQUIREMENTS

5.1. The issue

The Clinical Trials Directive, and its implementing guidelines, has brought in regulatory obligations and restrictions which, in some cases, are widely considered as not matching practical considerations and requirements.

5.2. Examples

5.2.1. Requirements not always risk-commensurate

Clinical trials as defined in the Clinical Trials Directive are very varied: The actual risk of a clinical trial for the participant in that trial depends on a wide range of factors, including:

- extent of knowledge and prior experience with the Investigational Medical Product (IMP);
- patient population is involved;
- whether or not the IMP is already authorised in the EU or elsewhere;
- whether the clinical trial is performed with an authorised medicine in approved indications or for other therapeutic uses; etc.

Thus, the risk for a clinical trial participant varies considerably depending on the actual circumstances of the clinical trial. Different types of trials carry different risks and thus require different regulatory safeguards. The Clinical Trials Directive does not discriminate sufficiently in this respect. Too often, it applies the "broad brush", and adopts a "one-size-fits-it-all" approach. This undifferentiated approach is visible in several areas. Examples include insurance requirements, safety reporting (including Suspected Unexpected Serious Adverse Reaction ''SUSAR'' reporting and yearly reporting of suspected Serious Adverse Reactions – "SARs"), labelling of the IMP, and monitoring of clinical trial sites and respective data collection process.

Consultation item n°9: Can you give examples for an insufficient risk-differentiation?

How should this be addressed?

Proposed response from PRN: A classic example of lack of risk differentiation is the use of Positron Emission Tomography (PET) radiotracers in clinical trials. A significant proportion of studies involving radiotracers are classified as clinical trials (e.g. where a radiotracer is being used to study a therapeutic that has been approved for an indication), so these need to meet the full standards of an IMP. PET radiotracers are administered as a single sub-therapeutic dose; indeed it is essential that radiotracers do not have any biological effect as this might perturb the behaviour of the process being studied. Furthermore, in this type of trial patients are closely monitored throughout the entire procedure (from before the radiotracer is injected until after the PET scan is completed). Consequently the insignificant pharmacological risk from the radiotracer and high standard of hospital care results in a very low level of risk. The CTD was originally primarily designed for therapeutic agents, which may be administered over an extended period without direct clinical supervision and which therefore have a much higher toxicity risk. Consequently, there is a very strong argument that trials involving PET radiotracers should have proportionate regulation that reflects the reduced risk in this type of trial. The best option would be to exclude academic sponsors from the CTD (item No 13) as obtaining a marketing authorisation is not usually an objective of this type of study. Alternative options could be to:

- Treat studies involving radiotracers as a separate category
- Revise the current version of the CTD (item No 11)

This would reduce the amount of administrative work, cost and time involved in meeting the CTD regulations, making EU PET trials more competitive on a global basis. It is very likely that there will be a steady increase in the number of PET trials during the next few years, which would help to justify changes to the CTD to ease regulations for PET trials in the EU.

5.2.2. Requirements not always adapted to the practical circumstances

To this adds that the Clinical Trials Directive establishes requirements which, albeit theoretically justified, are difficult to meet in practice. The most important aspect concerns the concept of a single sponsor. The Clinical Trials Directive is based on the concept of one single sponsor per (multi-national) clinical trial. This concept is meant to ensure that national competent authorities have a unique addressee for requests for information regarding a multi-national clinical trial. While this is a very legitimate objective, in practice, the solution of a "single sponsor" creates major difficulties: It is difficult for sponsors, in particular "academic"/"non-commercial" sponsors, to take responsibilities for clinical trials performed in another Member State. Equally, it is difficult for national competent authorities to enforce the Clinical Trials Directive vis-à-vis sponsors located in another Member State.

Consultation item n°10: Do you agree with this description? Can you give other examples?

Proposed response from PRN:
Yes, we agree with this description.
One solution would be to have a lead academic/non-commercial sponsor in each country that is participating in a multi-country trial.

5.3. Weaknesses

The consequences of these shortcomings are increased costs for conducting clinical research in Europe, while these costs are not necessary in order to achieve the objective of the Clinical Trials Directive, i.e. patient safety, ethical soundness of the clinical trial, and quality of research.

Moreover, these issues create disincentives to conduct clinical research in the EU. This consequence is felt in particular by so-called "academic"/"non-commercial" sponsors. While no clear definition exists, "academic"/"non-commercial" sponsors usually do not hold a marketing authorisation and do not intend to apply for it (as is the case with pharmaceutical companies). Clinical trials sponsored by "academic"/"non-commercial" sponsors are not necessarily performed with the intention to generate data to support an application for a marketing authorisation of a medicinal product.

The long-term consequence is that patients are deprived of innovative treatments and the competitiveness of European clinical research is reduced.

5.4. Options to address this issue

5.4.1. Review of existing implementing guidelines

Following the adoption of the Clinical Trials Directive, the Commission and the Agency, in close cooperation with Member States and stakeholders, have developed – in accordance with the mandate given by the co-legislator – implementing guidelines on the various provisions of the Clinical Trials Directive. These guidelines are very technical and extensive and published in Volume 10 of "EudraLex - The rules governing medicinal products in the European Union".

This option would involve a revision of some of these implementing guidelines in order to ensure that the implementing rules would be more risk-adapted. This would address the following aspects in particular:

- The rules for safety reporting;
- The rules for labelling of the IMP;
- The details of the rules for reporting of SUSARs;
- The content of the clinical trial application.

However, this option would not address issues which are directly vested in Community legislation, such as requirements for insurance, the requirement of a single sponsor per trial, and certain rules for reporting.

Therefore, this option could also be complementary to a more far-reaching change of applicable rules, thus addressing regulatory shortcomings in the interim.

Consultation item n°11: Can a revision of guidelines address this problem in a satisfactory way?

Which guidelines would need revision, and in what sense, in order to address this problem?

Proposed response from PRN: A revision of guidelines could help to stimulate PET research in the EU. Any of the following modifications would be beneficial for PET trials:

- Revise guidelines so that well-established radiotracers (ie those that have been used in several clinical trials by multiple research centres with no significant adverse effects), no longer need to be classified as IMP's
- Relax GMP requirements for radiotracers used for academic studies. For example, for PET tracers only a very small amount of Active Pharmaceutical Ingredient (API) is required and GMP manufacture is therefore often prohibitively expensive on a 'per gram' basis. The requirement for GMP manufacture of API's for academic studies does not contribute significantly to the safety or robustness of such trials and it would therefore be appropriate to relax this requirement for trials of agents for which a marketing authorisation is not going to be sought.
- Reduce burden of application process by allowing inclusion of data/information from previous applications using the same radiotracer – this would reduce duplication of effort (for example there could be a standard application for trials involving ^{18}F-FDG, ^{18}F-FLT etc).
- A reduction in the overall regulatory burden would be welcomed by the PET community

5.4.2. Review of the existing Directive and adaptation of the requirements to practical necessities

This option would consist in reviewing the Clinical Trials Directive in order to adjust it to experiences.

The advantage of this option would be that issues can be addressed which are grounded in the legislation itself, i.e. areas where changes to implementing guidelines would not have effect.

Consultation item n°12: In what areas would an amendment of the Clinical Trials Directive be required in order to address the issue?

If this was addressed, can the impacts be described and quantified?

Proposed response from PRN: The major suggested change to the guidelines would be to adopt a risk adapted approach. Most radiotracers are given such that they do not perturb the system they are studying. They are normally given in doses far less than 100 μg and thus are often present at lower concentrations that some contaminants in therapeutic medicines.
The authorities should therefore be able to reduce toxicology data to a minimum, reduce the collected data to a minimum data set when studying a novel radiopharmaceutical. There should be true sharing of information across the EU so that investigators do not need to duplicate work that has already been registered with a competent agency in another country. Perhaps the data could be shared via a common database; an assigned number could be quoted by other researchers and enshrined in the directive.
A lighter regulatory touch would do much to increase the competitiveness of the Academic community in the EU in the face of severe competition from other countries. It would be possible to ensure compliance with safety requirements and data quality by conforming with a much simpler procedural framework.

5.4.3. Review of the existing Directive and excluding clinical trials of "academic" sponsors from the scope of the Directive

This option would mean an outright exclusion of so-called "academic" sponsors from the rules of the Clinical Trials Directive. This would mean that national rules set by Member States would apply. This would also mean that, in accordance with the Community legislation set out above, results of these clinical trials cannot be referred to in the framework of an application for a marketing authorisation in the EU.

Consultation item n°13: Would you agree to this option and if so what would be the impact?

Proposed response from PRN: Much of the information required to support a Clinical Trials Authorisation, particularly that relating to pharmaceutical development and manufacture of the IMP is required in anticipation of a future marketing authorisation for the drug. However this does not happen for the great majority of Academic trials and consequently generation of this information consumes unnecessary time and expense and represents a very considerable hurdle to implementation of such trials. Academic studies, trials sponsored by charities and phase 0 trials should therefore be exempted from the CTD. Alternatively, a clear distinction should be made between the requirements for trials of agents for which a marketing authorisation is to be sought and those for which it is not.
The prime requirements for such studies are 1) the safety of the trial subjects and 2) the robustness of the scientific data generated by the trial. These requirements are adequately covered by national guidelines.

Therefore, we would agree that the proposed amendment would be a good option, as the general aim of the EU academic PET community is not to apply for a marketing authorisation. The amendment should, however, also exclude trials sponsored by charities and phase 0 trials. Academic centres aiming to apply for a marketing authorisation could choose to comply with CTD regulations.
The proposed amendment could make it easier (e.g. reduced time, effort and resources required) to obtain approval for several types of PET study, helping to remove an obstacle that is currently impeding progress in the PET field:
1. To qualify new PET tracers (accumulate evidence to link a biomarker with underlying biology, and with clinical endpoints to understand their utility and limitations).
2. Perform diagnostic trials using either a new radiotracer or an established radiotracer in a new indication.
3. Carry out PET studies using established radiotracers in indications where a therapeutic is already approved.

On the other hand it should still be necessary for academic centres to conform to the CTD for drug trials where radiotracers are employed to support development of new agents, but the object of study is the new therapeutic.