Public Consultation Paper: Assessment of the Functioning of the Clinical Trials Directive 2001/20/EC

National Institute for Health Research (NIHR CRN) and UKCRC Registered Clinical Trials Units Response

The National Institute for Health Research Clinical Research Network (NIHR CRN) supports clinical research by facilitating the conduct of trials and other well-designed studies within the NHS. The NIHR Clinical Research Network (NIHR CRN) in England is one of the four networks that comprise the UK Clinical Research Network (UKCRN). The NIHR CRN Coordinating Centre also coordinates the UKCRC activities in relation to Clinical Trials Units (CTUs) including the UKCRC CTU Registration Process. This response is a collation of responses from the NIHR CRN and the UKCRC Registered Clinical Trials Units.

Consultation 1. Can you give examples for improved protection (of patients)? Are you aware of studies / data showing the benefits of the Clinical Trials Directive?

- Improved patient protection through improved knowledge of the principles of GCP for those conducting non-commercial trials.
- Increased transparency and clearer delegation of responsibilities with the requirement for trial sponsors to have written contracts defining these responsibilities.
- Improved timelines and consistency of ethical review by the UK National Research Ethics Service (NRES).
- But there is still some way to go. The objectives of the Directive have gone some way to being met but the administrative burden and costs associated with this have increased exponentially without necessarily contributing to improved patient safety and the reliability of results. Also lack of harmonisation across Europe has not been achieved.

Key Issue 1. Multiple and divergent assessments of clinical trials.
Consultation 2. Is this an accurate description of the situation? What is your appraisal of the situation?
There have been limited numbers of pan-European trials led by UK investigators since the EU CTD was implemented as a result of the complexity, bureaucracy, risk and increased cost associated with running trials across Europe under the EU CTD and so there is limited experience of differences in the trial authorisation process across the different Member States. Rather than harmonising trial conduct across Europe, the EU CTD has made multi-national trials more difficult to manage. Lack of harmonisation for clinical trial applications, inconsistency between ethics committee structures and functions, and divergent reporting requirements have served as a deterrent to non-commercial organisations from conducting trials internationally if they can be conducted in the UK only.

Consultation 3. Is this an accurate description? Can you quantify the impacts? Are there other examples of consequences?
There have been limited numbers of pan-European trials led by UK investigators since the EU CTD was implemented as a result of the complexity, bureaucracy, risk and increased cost associated with running trials under the EU CTD and so there is limited experience of trial authorisation differences across the different Member States.

Consultation 4. Can you give indications / quantifications / examples for the impact of each option? Which option is preferable? What practical / legal aspects would need to be considered in further detail?

There is no support for a centralised procedure from the NIHR CRN although it is acknowledged that a workable solution to streamlining authorisations is required. Since many clinical trials only involve one Member State, the presence of an experienced NCA is essential and therefore a system based on the Voluntary Harmonisation Process would appear to be the most promising.

Consultation 5. Can you give indications / quantifications / examples for the impact of each option? Which option is preferable? What practical / legal aspects would need to be considered in further detail?

- *One stop shop for submission of assessment dossier*. In terms of how the MHRA and NRES work within the UK, streamlining the application process would reduce the administrative burden and minimise the risk of conflicting issues arising during the review process. However, the ethical review process is currently free of charge within the UK and this option would be resisted if it were to invoke a charge as with the review of the MHRA.
- *Strengthening networks of national Ethics Committees involved in multinational trials.* Strengthening networks across the EU is highly desirable.

Key Issue 2. Inconsistent implementation of the Clinical Trials Directive
Consultation 6. Is this an accurate description of the situation? Can you give other examples?

Yes the description is accurate. Other examples are:

- Defining definitions of substantial amendments across borders and outside the EU.
- Inconsistent requirements for indemnity arrangements has prevented collaboration with countries that require non negligent indemnity for all trials.
- The pharmacovigilance and Eudravigilance system requires a full review to minimise the duplicate reporting of SUSARs by collaborating organisations.
- Eudravigilance reporting is an issue for non-commercial organisations because it is not easy to maintain a critical mass of trained and experienced staff to be able to do this consistently when the volume of work is very small for any one organisation.

Consultation 7. Is this an accurate description? Can you quantify the impacts? Are there other examples of consequences?

This is an accurate description. Other examples are:

- Provision of information inappropriate to patients (in terms of content relevance or wording) or at an inappropriate time. For example different interpretation of legislation has led to differing requirements for re-consenting patients to trials and approved trial documentation. Specific examples include where patients have been required to re-consent to new versions of a summary of product characteristics and all new versions of consent forms, regardless of the changes.
- Immediately following the implementation of the Directive some research teams within the UK witnessed an increase in SUSAR reports that did not meet the definition of 'unexpected'. Training staff in the terminology has resulted in fewer incorrect reports.
- Insufficient patient protection. The inconsistent implementation and reporting requirements for serious breaches will lead to an inability of the Regulatory Authorities to respond appropriately / consistently across borders.

Consultation 8. Can you give indications / quantifications / examples for the impact of each option? Which option is preferable? What practical / legal aspects would need to be considered in further detail? In particular, are the divergent applications really consequence of transposing national laws, or rather their concrete application on a case-by-case basis?

Reviewing the Clinical Trials Directive with a view to clarifying provisions, where necessary would be preferable for the following reasons:

- It is the way in which information is provided and therefore interpreted that is the issue not the reluctance of users to apply the principles and rules of the Directive
- Review of guidelines through user groups etc would be a way forward and is already being adopted by the MHRA.

Key Issue 3. Regulatory framework not always adapted to the practical requirements

The NIHR CRN are fully supportive of a risk based approach to regulation that takes into account the practical requirements of conducting academic research within the NHS.

Consultation 9. Can you give examples for an insufficient risk – differentiation? How should this be addressed?

- Many non-commercial trials are designed to follow clinical practice in so far as is possible to ensure generalisability of the results. This means that in many cases where widely used drugs or combinations are being compared the inherent overall risk of the trial is the same or only marginally higher than that of routine practice and therefore the implementation of a 'one-size fits all' set of rules for regulation is inappropriate. There are risks involved in taking any medication whether or not this is within a clinical trial and so a better approach would be to identify whether the risk: benefit ratio of the trial differs significantly from that of routine practice rather than the one size fits all approach.
- There is no discrimination in the ways that IMPs with different risk: benefit ratios are handled in clinical trials and often the requirements of the Directive (or local Regulations) result in excessive additional requirements for handling an IMP where the IMP would usually be available over the counter or off the shelf. This dramatically increases pharmacy and CTU workload but sometimes has little influence on the inherent risks to the patient within the clinical trial and often requires additional processes than those that would occur in routine practice. No allowances are made for non-commercial sponsors who have no involvement in the manufacture or distribution of IMPs.
- Specific examples of such issues in clinical trials are:
    - Additional labelling and accountability for IMPs that in routine practice (and therefore in the trial) may be dispensed over the counter (e.g. statins).
    - Additional labelling, accountability and manufacturing requirements for products that can be bought off the shelf (e.g. vitamin D).
    - Pregnenolone is a widely used food supplement but would be classed as an IMP in a clinical trial. Sourcing and manufacturing this substance to the required standards resulted in the cost of the trial being unviable.
    - In many cancer trials, the control treatment is a drug or combination of drugs used within their licensed indication. The experimental treatment is commonly a drug that is already licensed for use in cancer, but not necessarily in the particular type of cancer, or combination or timing of use (i.e. before surgery, after surgery etc) that is covered by the licence. For trials of chemotherapy treatment, both the control and experimental treatments may involve several drugs used in combination, all of which are known to have detailed and documented side effect profiles. Many trials test IMPs within their marketing authorisation against IMPs that are licensed but not in the precise setting being used. The IMPs do not require particular manufacture or packaging, but Annex 13 labelling is required together with detailed accountability records and destruction logs which places unnecessary administrative burden on participating sites and the Sponsor without improving patient safety.
    - The requirements for handling the IMP within a pharmacy are not risk commensurate and often lead to excessive requirements for overlabelling, tracking IMPs and recording batch number on a per patient basis, reconciliation

of labels (advice given by a GCP Inspector), drug reconciliation, notification and procedures for temperature discursions, ring fencing and procedures for product recall above those required for the same drug being used in general practice.

- IMPs that are not physically handed to the patient to administer themselves should not require any specific labelling if used according to a recognised dose and schedule.
- Accountability and destruction logs should only be required for IMPs that require Annex 13 labelling, and where they are dispended from hospital pharmacies from stock specifically supplied for use in the clinical trial.
- The definition of a Non-Investigational Medicinal Product (Non IMP) for IMPs used within a clinical trial did not dramatically reduce the required workload for handling non IMPs as was originally expected and instead just incorporated an additional layer of administration and resource requirement but for no additional gain to patient safety or trial reliability. In addition the upgrade of comparator products to IMPs even when they are being used according to routine practice is not justified in terms of protecting patient safety.
- Guidance on acceptable levels of on-site monitoring based on the risk of the trial (design and to patients) is not available. For example Ireland requires 100% source data verification monitoring which is not the approach that is being undertaken in other participating countries and is not based on the risks of the trial. There needs to be clearer recognition given to central statistical monitoring, and clarity that the level of on-site monitoring should reflect the risks for the individual trial.
- A more pragmatic approach to the completion of application documentation, categorising substantial amendments and also a reduced burden of paperwork for simple amendments such as the change of address of a Principal Investigator is recommended in line with a risk based approach.
- The requirement to notify ethics committees and other investigators of SUSARs as they occur within the trial, rather than when an assessment of whether the risk: benefit profile has been changed can be confusing.
- Implementation of the principles of GCP on a practical level also requires review

Consultation 10. Do you agree with this description? Can you give other examples?

Other examples of requirements not always adapted to the practical circumstances:

- The production of an IMP dossier for well known products such as food supplements is financially prohibitive for academic sponsors and could prevent justified research that may benefit large groups of the patient population. .
- Pharmacovigilance requirements are not risk commensurate and specifically do not take into account the roles of trial oversight committees. The immediate review of individual SAEs is a very poor way of assessing the cumulative adverse effects of the trial intervention; this role is best served by the Data Monitoring Committee for the trial within timelines for review agreed according to the risk of the trial.
- The Directive (and supporting Guidance) requires an Investigators Brochure for an IMP being used outside its licensed indication. For a drug that is being used outside it's licensed indications but is used extensively in routine practice this may mean that the Investigator Brochure is not as up to date or regularly updated as the Summary of Product Characteristics.

Consultation 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?

A revision of the guidelines could address this problem if they are clearly written and reviewed appropriately by key stakeholders. Safety reporting, SUSAR reporting and IMP labelling guidelines should be reviewed.

Consultation 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?
No comment

Consultation 13. Would you agree to this option and if so what would be the impact?
This option is not acceptable to the NIHR CRN; the objectives of the EU Directive were commensurate with principles that should apply to all trials involving drugs and human patients regardless of the sponsor and whether the application will be used for a marketing authorisation. This would also result in the conduct of multinational academic trials becoming even harder if each country had different rules governing the conduct of these trials and would also mean that data generated from key trials could not be used to support marketing authorisations for new indications.

Many of the trials being conducted by academic sponsors are of a lower risk than those conducted by pharmaceutical companies. All trials regardless of sponsor, should be subject to a risk based approach to regulation.

Key Issue 4. Adaptation to peculiarities in trial participants and trial design
Consultation item 14. In terms of clinical trials regulation, what options could be considered in order to promote clinical research for paediatric medicines, while safeguarding the safety of the clinical trial participants?
No comment

Consultation item 15. Should this issue be addressed? What ways have been found in order to reconcile patient's rights and the peculiarities of emergency clinical trials? Which approach is favourable in view of past experiences?
No comment

Key Issue 5. Ensuring compliance with GCP in clinical trials performed in third countries
Consultation 16. Please comment? Do you have additional information, including quantitative information and data?
No comment

Consultation 17. What other options could be considered, taking into account the legal and practical limitations?
No comment