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Improving health worldwide

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Revision of the 'Clinical Trials Directive' 2001/20/EC
Concept Paper Submitted for Public Consultation
European Commission SANCO/C/8/PB/SF D(2011) 143488

1. COOPERATION IN ASSESSING AND FOLLOWING UP APPLICATIONS FOR CLINICAL TRIALS

1.1 Single submission with separate assessment a. single submission Consultation item n°1: Do you agree with this appraisal? Please comment.
Yes, a single submission would be more efficient, cost-effective and timely.

b. separate assessment Consultation item n°2: Do you agree with this appraisal? Please comment.
Yes, separate assessment would be inefficient and leads to the same issues that occur presently whereby CAs in different member states review the study with differing criteria which results in conflicting requests for amendments.

1.2. Single submission with subsequent central assessment Consultation item n°3: Do you agree with this appraisal? Please comment.
Central assessment would be more efficient, therefore we do not agree with this assessment. The number of applications should not influence the choice of system. Although it is recognised that each Member State has different methods of ethical review, the standards should not vary across the EU.

1.3. Single submission with a subsequent 'coordinated assessment procedure' *1.3.1. Scope of the CAP* Consultation item n°4: Is the above catalogue complete?
Yes

Consultation item n°5: Do you agree to include the aspects under a), and only these aspects, in the scope of the CAP?
Yes

1.3.2. Disagreement with the assessment report Consultation item n°6: Which of these approaches is preferable? Please give your reasons.
Option 2 (vote on the issues) would be the preferable option as it allows all Member States to voice their opinion and to agree to a majority vote.

1.3.3. Mandatory/optional use Consultation item n°7: Which of these three approaches is preferable? Please give your reasons.
Option 2 (mandatory for all multi-national trials) would be preferable as it is simplest to have a single system applicable to all studies. It may be worthwhile having a pilot phase however, to ensure that sponsors and Member States have the opportunity to try out the process and evaluate the procedures.

1.3.4. Tacit approval and timelines Consultation item n°8: Do you think such a pre-assessment is workable in practice? Please comment.
Yes, but who would be responsible for determining whether the trial was type A (minimal risks). If it is to be the Sponsor, would there be a check to ensure that it really is type A?

2. BETTER ADAPTATION TO PRACTICAL REQUIREMENTS AND A MORE HARMONISED, RISK-ADAPTED APPROACH TO THE PROCEDURAL ASPECTS OF CLINICAL TRIALS

2.1. Limiting the scope of the Clinical Trials Directive *2.1.1. Enlarging the definition of 'non-interventional' trials* Consultation item n°9: Do you agree with this appraisal? Please comment.
Yes, it would be better to simplify the Directive rather than enlarge the definition of non-interventional trials as this would inevitably lead to more confusion.

2.1.2. Excluding clinical trials by 'academic/non-commercial sponsors' from the scope of the Clinical Trials Directive Consultation item n°10: Do you agree with this appraisal? Please comment.
Yes. From our perspective (an academic institution), we would be reluctant for all clinical trials for which we are sponsor, be omitted from the jurisdiction of the EU Clinical Trials Directive as data from our studies may be used for commercial purposes, as well, although we mostly use products with existing marketing authorisations, there may still be sufficient risks involved should we use the product outside the licensing requirements or in a new population or in combination with other products. Rather, it would be more useful to apply regulation on the basis of the risk of a study and not type of sponsor.

2.2. More precise and risk-adapted rules for the content of the application dossier and for safety reporting

Consultation item n°11: Do you agree with this appraisal? Please comment.

Yes

Consultation item n°12: Are there other key aspects on which more detailed rules are needed?

Yes, other aspects that would be useful to have a single set of rules would include: import/export of biological samples, import/export of Investigational Medicinal Products.

2.3. Clarifying the definition of 'investigational medicinal product' and establishing rules for 'auxiliary medicinal products'

Consultation item n°13: Do you agree with this appraisal? Please comment.

Yes

2.4. Insurance/indemnisation

Consultation item n°14: Which policy option is favourable in view of legal and practical obstacles? What other options could be considered?

Neither proposal is practicable. Ideally it should be the Sponsor's decision as to the level of indemnity required for a study as even the low-risk studies may require compensation in the event of harm. Member States should have similar insurance requirements, or be explicit in what will or will not be required.

2.5. Single sponsor

Consultation item n°15: Do you agree with this appraisal? Please comment.

Yes

2.6. Emergency clinical trials

Consultation item n°16: Do you agree with this appraisal? Please comment.

The requirement for informed consent to be obtained (whether from the patient, their personal legal representative or professional legal representative) before a patient can be enrolled in an emergency clinical trial remains a major impediment to finding safe and effective treatments for patients in life threatening emergency situations. There is now empirical evidence that the delay in the initiation of emergency treatment arising from the need to obtain informed consent has resulted in avoidable mortality and morbidity in emergency care trials, and that this delay results in underestimates of treatment effects (1). The proposed amendments go some way to resolving these problems and should allow for the enrolment of patients in emergency situations.

However, the proposal that "informed consent would have to be obtained as soon as possible from the parents/legal representative (in case of adults) or the trial subject, whichever is sooner," is often neither ethical nor practical in the context of a clinical trial for the following reasons:

In emergency care trials of acute interventions where there is a high mortality rate (e.g. traumatic brain injury or acute severe bleeding), parents or legal representatives may then be asked to give retrospective informed consent for inclusion of a patient in a clinical trial after a patient has died and after the patient has been

included and after treatment had been administered. What exactly are the parents or legal representatives consenting to, and why?
Furthermore, for consent to be truly valid and informed it requires the following:

[1] Voluntary: free from "coercion" and from unfair persuasions and inducements
[2] Capacity: ability to make health care decisions
[3] Disclosure: involves providing representative with the information needed to understand a procedure. This information includes the nature and purpose of the treatment, as well as its risks, potential benefits, and any available alternatives
[4] Understanding: requires that the representative to comprehend the information given and appreciates its relevance to the patient's individual situation
[5] Decision: refers to the representative's authorization allowing the trial team to execute the proposed treatment

Is it appropriate to ask relatives of a critically ill or deceased patient to give informed consent "as soon as possible?" Why would a legal representative be willing to take responsibility in this context? It is nonsense to ask anyone for permission to do something that has already been done.
If the patient recovers competence and the treatment has already been given what would the patient be asked to give consent for?

If retrospective informed consent cannot be obtained from patients who have already been enrolled in an emergency clinical trial because they have died and their relatives/legal representative are unavailable or unwilling to give consent, it is unclear how the data from these patients should be managed. If their data are excluded from the analysis this would threaten to the validity of the trial results and could result in future patients being denied effective treatments or being given useless or harmful treatments.

The threat to the validity of clinical trials from post randomization exclusions has been recognized by the FDA whose guidance acknowledges that in certain circumstances the retention of clinical trial data is allowed even where consent has been withdrawn:

"Data collected on study subjects up to the time of withdrawal must remain in the trial database in order for the study to be scientifically valid. If a subject withdraws from a study, removal of already collected data would undermine the scientific, and therefore the ethical, integrity of the research. Such removal of data could also put enrolled subjects, future subjects, and eventual users of marketed products at an unreasonable risk. Finally, removal of data would fundamentally compromise FDA's ability to perform its mission, to protect public health and safety by ensuring the safety and effectiveness of regulated products."

Proposed solution

Time limited interventions

Patients in emergency clinical trials who are unable to give informed consent should be regarded as an exception to the general expectation that informed consent should be sought from potential participants in clinical trials. If the responsible ethics committee considers that a patient in such circumstances can be enrolled in a clinical trial, then its approval will have been both for enrolment and for the use of the resulting data. Patients and relatives should be given information about the trial but because the trial intervention has already been given they should not be asked to give retroactive consent to take part. The patient's data should be included in the analysis because he or she was enrolled into the trial in a legally and ethically appropriate manner. Future patients, and even the same patient if the emergency situation recurs, could be put at risk if the data were to be excluded.

On-going trial treatments

If a patient regains the capacity to give informed consent, or a relative becomes available, and the treatment is on-going, then informed consent to further treatment can be sought. If it is withheld, then the treatment should be stopped, but the data should be included in the analysis.

References:

1. http://download.thelancet.com/flatcontentassets/pdfs/S0140673611603176.pdf

2. http://www.fda.gov/downloads/regulatoryinforamtion/guidances/ucm126489.pdf

3. ENSURING COMPLIANCE WITH GOOD CLINICAL PRACTICES IN CLINICAL TRIALS PERFORMED IN THIRD COUNTRIES

Consultation item n°17: Do you agree with this appraisal? Please comment.
Yes, although it is unclear of what is expected by “supporting capacity building in third countries”.

4. FIGURES AND DATA

Consultation item n°18: Do you have any comments or additional quantifiable information apart from that set out in the annex to this document? If so, you are invited to submit them as part of this consultation exercise
Funding bodies are increasingly expecting academic trials to involve patients and the public in the designing of our trials, especially allowing them to decide what information is appropriate for information leaflets. This inevitably leads to conflict as there is a strict list of what needs to be included according to GCP; however the public and patients often want less detail and more relevant information. The RECRUIT study (see http://www.hta.ac.uk/execsumm/summ1515.shtml) states “**All parties valued the face-to-face discussion more highly than the participant information leaflets (PILs), and wanted shorter, and less complex, written information”.** How to reconcile what patients deem important with what is expected in the EU Directive and GCP?

Submitted on behalf of the clinical trials sub-committee
LSHTM