



Inspectie voor de Gezondheidszorg  
Ministerie van Volksgezondheid,  
Welzijn en Sport

# Voor gerechtvaardig vertrouwen in verantwoorde zorg

## REVISION OF THE 'CLINICAL TRIALS DIRECTIVE' 2001/20/EC

Reflections of a GCP-inspector on  
some of the preliminary appraisals.

..... and some room and time for your opinion



## Consultation item no. 9:

### *2.1.1. Enlarging the definition of 'non-interventional' trials*

#### Preliminary appraisal:

Rather than limiting the scope of the Clinical Trials Directive through a wider definition of 'non-interventional trial', it would be better to come up with harmonised and proportionate requirements which would apply to all clinical trials falling within the scope of the present Clinical Trials Directive.

See in particular points 2.2 to 2.5.



## Consultation item no. 10:

*2.1.2. Excluding clinical trials by 'academic/non-commercial sponsors' from the scope of the Clinical Trials Directive*

### Preliminary appraisal:

Rather than limiting the scope of the Clinical Trials Directive, it would be better to come up with harmonised and proportionate requirements for clinical trials.

These proportionate requirements would apply independently of the nature of the sponsor ('commercial' or 'academic / non-commercial').

See in particular points 2.2 to 2.5.



## Consultation item no. 11:

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

### Preliminary appraisal:

This approach would help to simplify, clarify, and streamline the rules for conducting clinical trials in the EU by providing one single, EU-wide, risk-adapted set of rules.



## ..... and what is the appraisal ?      Annexes !

To address this need, sufficiently detailed provisions on these topics could be included in Annexes to the basic legal act. The Commission could, when necessary, update them by means of delegated acts. In drawing up these Annexes, one would have to take into account:

- the risk to trial subject safety compared to normal clinical practice;
- the risk to data reliability and robustness;
- international harmonisation work, such as the guidelines of the International Conference on Harmonisation ('ICH').



## Consultation item no. 13:

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

### Preliminary appraisal:

This combined approach would help to simplify, clarify, and streamline the rules for medicinal products used in the context of a clinical trial.



## The combined approach:

- The definition of IMP could be changed and clarified by narrowing it as follows: *'A medicinal product which falls within the definition of Article 3(3) of Directive 2001/83/EC, and which is being tested or used as reference in a clinical trial.'* This would ensure that only the medicines that are the object of the study are covered by the requirements for IMP;
- The notion of 'auxiliary medicinal product', covering all other medicinal products used in the context of the clinical trial, could be introduced: *'A medicinal product as referred to in Article 3(3) of Directive 2001/83/EC which is not an investigational medicinal product'*;



## Consultation item no. 14:

### *2.4. Insurance/indemnisation*

Which policy option is favourable in view of legal and practical obstacles? What other options could be considered?

- Removing insurance/indemnisation requirements for low-risk trials:  
This policy option would remove the insurance requirement for clinical trials which typically pose a low risk for trial subjects (see point 1.3.4); or
- Optional indemnisation by Member State:  
This policy option would put Member States under an obligation to provide for an indemnisation for damages incurred during clinical trials performed in their territory, taking account the national legal system for liability.  
In view of the damages arising today (see annex), the burden on national budgets would be minimal.



## Consultation item no. 15:

### *2.5. Single sponsor*

#### Preliminary appraisal:

In view of the above, option 1 may be preferable  
Two options could be considered:

- Option 1: maintaining the concept of a single sponsor;
- Option 2: allowing for a concept of 'multiple sponsorship'/'joint sponsorship'/'shared sponsorship'/'co-sponsorship', where each sponsor is 'responsible' for a specific task or for the conduct of the trial in a Member State.



## However, there are two clear 'restrictions'

Provided that:

- it is clarified that the 'responsibility' of the sponsor is without prejudice to the (national) rules for liability; and
- it is ensured that the regulatory framework for clinical trials in the EU is truly harmonised (see point 2.2).



## Consultation item no. 16:

### *2.6. Emergency clinical trials*

In view of these texts, the Clinical Trials Directive could be amended to the effect that the informed consent and the information from the investigator may take place during or after the clinical trial under the well-defined conditions.

### Preliminary appraisal:

This could be a viable option in order to address this type of research and bring the regulatory framework in line with internationally-agreed texts.



## What are those well-defined conditions ?

- The trial subject is not in a state to give informed consent;
- The physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population;
- Because of the urgency of the situation, it is impossible to obtain informed consent from the parents/legal representative (in case of adults) in accordance with the Clinical Trials Directive, and it is impossible to give the information, as provided in the Clinical Trials Directive;
- The trial subject has not previously expressed objections known to the investigator.



## Consultation item no. 17:

### *3. Ensuring compliance with Good Clinical Practices in clinical trials performed in third countries*

As set out in the 2009/10 public consultation paper, any disregard of the rules that protect clinical trial participants is unacceptable and calls for determined action – independently of where the clinical trial has been performed. The Commission is committed to ensuring that the fundamental ethical rules for clinical trials are applied everywhere.

Any weakening of the standards with regard to third countries would be in contradiction to the fundamental principles of human rights and dignity and their universal guarantee and protection, to which the EU is fully committed.



## Preliminary appraisal:

In view of the jurisdictional limits, particular consideration should be paid to clinical trials in third countries where the data is submitted in the EU in the framework of the authorisation process of

- Clinical trials; and
- Medicinal products

In addition, in order to increase transparency of clinical trials performed in third countries the legislation could provide that the results of these clinical trials are only accepted in the context of a marketing authorisation process in the EU **if the trial had been registered in the EU clinical trials database *EudraCT*** and thus be published via the public EU-database *EudraPharm*.<sup>20</sup>



Regarding the **authorisation process for a clinical trial**, this is currently addressed in point 2.7.2.4. of the detailed guidance CT-1,14 which provides that:

*'All studies [submitted in the authorisation process of a clinical trial] should have been conducted in accordance with the principles of Good Clinical Practice (GCP).'*

*To this end, the applicant should submit the following:*

— *a statement of the GCP compliance of the clinical trials referred to,*  
— *where a clinical trial referred to has been performed in third countries, a reference to the entry of this clinical trial in a public register, if available. Where a clinical trial is not published in a register, this should be explained and justified.'*



Regarding the **marketing authorisation process of medicines**, this is addressed in point 8 of the introduction to the Annex of Directive 2001/83/EC, 15 which provides that:

*'All clinical trials, conducted within the European Community, must comply with the requirements of Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.*

***To be taken into account during the assessment of an application, clinical trials, conducted outside the European Community, which relate to medicinal products intended to be used in the European Community, shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC.***

***They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki.***



Both provisions, as well as implementation work could be further supported and supplemented through the following:

- Codifying, in the revised legislative framework,<sup>18</sup> the provision in point 2.7.2.4. of the detailed guidance CT-1 (see point above); and
- Further supporting capacity building in third countries where the regulatory framework for clinical trials, including its enforcement is weak.

**In addition, in order to increase transparency of clinical trials performed in third countries the legislation could provide that the results of these clinical trials are only accepted in the context of a marketing authorisation process in the EU if the trial had been registered in the EU clinical trials database *EudraCT* and thus be published via the public EU-database *EudraPharm*.<sup>20</sup>**



# Thank you for your attention

On behalf of The Clinical Trials Unit  
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