Premessa

Le sperimentazioni cliniche sono studi condotti su soggetti umani per valutare gli effetti di uno o più medicinali. La loro regolamentazione pone pertanto problematiche medico-scientifiche, etiche ed economiche di notevole impatto ed attualmente, nell'Unione Europea, la relativa normativa è armonizzata dalla Direttiva 2001/20/CE. In Italia, il D.Lgs. 211/2003 (entrato in vigore il I gennaio 2004) ha recepito questa direttiva europea, che ora è pienamente a regime.

Nel 2008, la Commissione Europea annunciò di voler iniziare una verifica del percorso fino ad allora intrapreso, valutando le diverse opzioni per migliorare l'implementazione della succitata direttiva, anche alla luce delle problematiche applicative emerse e della dimensione ormai globale in cui si devono intraprendere le sperimentazioni cliniche.

Dopo una prima consultazione pubblica nel 2010, nell'iter verso una revisione della Direttiva 2001/20/CE, il 9 febbraio 2011, la commissione ha aperto un'ulteriore consultazione pubblica sui possibili scenari futuri pubblicando un *concept paper submitted for public consultation* dal titolo "REVISION OF THE 'CLINICAL TRIALS DIRECTIVE' 2001/20/EC" (**http://ec.europa.eu/health/files/clinicaltrials/concept_paper_02-2011.pdf**).

Le risposte al documento andavano inviate entro il 13 maggio 2011 e numerose sono stati gli interventi di varie società scientifiche ed istituzioni (tra cui anche l'Agenzia Italiana del Farmaco). Non sono mancati interventi su diverse autorevoli riviste, come ad esempio quello su alcuni aspetti relativi all'ottenimento del consenso informato negli studi clinici che riguardano situazioni di emergenza (I. Roberts et al., Lancet 2011; 377: 1071-1072).

Sono riportate qui di seguito le risposte che, punto per punto, ha fornito il gruppo di lavoro della SIF (sezione Clinica), cui hanno partecipato diversi farmacologi clinici, tra cui Maria Del Zompo, Silvano Cella, Carlo Patrono e i membri del Consiglio Direttivo Antonello Di Paolo e Fabrizio De Ponti.

Le risposte fornite dal gruppo di lavoro, sono riportate inserite nel testo del documento, e sono identificabili dall'essere riportate in un riquadro (oltre che dal carattere e dalla formattazione diversa). Il documento completo contiene note e una appendice, che non sono qui riportate.

Response to: Concept Paper of February 9th, 2011 submitted for public consultation by the European Commission on the Revision of the "clinical trials directive" 2001/20/ec

Submitted May 11, 2011 by the ITALIAN SOCIETY of PHARMACOLOGY – Section of CLINICAL PHARMACOLOGY

To: sanco-pharmaceuticals@ec.europa.eu.

***

*The **Italian Society of Pharmacology** (SIF) was founded in 1939. In 1996 it was recognised as a non-profit scientific association by the Ministry of the University, Scientific and Technological Research. It is a member of IUPHAR and EPHAR (Federation of the European Pharmacological Societies). The present membership of SIF consists of 1169 ordinary members, 12 honorary members and 20 supporting members.*

The Society has a permanent office in Milan and is managed by a President, a President elect and a Steering Committee of 8 members. The Society includes a Section of Clinical Pharmacology which is managed by a Co-ordinator and a Steering Committee reporting to the President.

SIF is an active and lively society, which has gradually changed from a typical learned society devoted mostly to the exchange of scientific information among its members to a kind of professional society, which, without severing the scientific roots which represent its "raison d'être", aims to promote pharmacology in Italy by fostering pharmacological education within the University, the National Health System and the general public, by supporting young pharmacologists with travel fellowships and grants and helping them to find jobs, and by collaborating with public authorities and private organisations in disseminating expert opinions on drug efficacy and side effects.
Over the past 15 years, several pharmacologists associated to SIF have been appointed members in ethics committees operating in Italy according to the Ministerial Decrees regulating clinical trial approval in Italy.

***

Brussels, 09/02/2011
SANCO/C/8/PB/SF D(2011) 143488

REVISION OF THE 'CLINICAL TRIALS DIRECTIVE' 2001/20/EC
CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

A. INTRODUCTION

The European Commission is planning to put forward, in 2012, a legislative proposal to revise the Clinical Trials Directive 2001/20/EC (**http://ec.europa.eu/atwork/programmes/docs/cwp2011_annex_en.pdf** . To assess the impact of this revision, a public consultation was held from 9 October 2009 to 8 January 2010 (the '2009/10 public consultation'). The responses, together with a summary of them, have been published on the 'clinical trials website' of 'Health and Consumers' Directorate-General (DG SANCO, **http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm**).

This concept paper is being put out for public consultation. (Practical information about the consultation is set out at the end of the paper). It presents:

- a 'preliminary appraisal' of which option appears to be the most suitable one to address some of the key concerns of the Clinical Trials Directive, on the basis of the current state of the impact assessment; and
- the main figures that are being used to evaluate the impacts of the different policy options.

It is not the purpose of this consultation paper to repeat the 2009/10 public consultation. Topics which have been explored extensively during that consultation are not again put forward for discussion. Rather, the purpose of this public consultation is

- to seek views on more concrete ideas on the issues that have been presented in a rather general way during the 2009/10 public consultation. Consequently, some issues looked at in this paper are of a more detailed and technical nature; and
- to verify with stakeholders the core data which forms the basis of the impact assessment (see point 4 of the consultation topics and Annex).

B. CONSULTATION TOPICS

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

The Clinical Trials Directive sets out common rules for the authorisation and regulatory follow-up of a clinical trial with the objective to protect clinical trial subjects and ensuring that the

results are credible.
The legislation does not provide for any mechanism whereby the application for the clinical trial is submitted jointly to all Member States concerned ('single submission'), nor does the legislation foresee that Member States concerned work together to assess or follow up the request for authorisation. Instead, the request for authorisation of a clinical trial is assessed independently by the various Member States concerned.

As a consequence,

- largely identical information has to be sent to several different Member States, which creates unnecessary administrative costs3; and
- the requirements set out in the Clinical Trials Directive are applied differently in the different Member States. While the broad concepts are identical, divergent and conflicting points of view can emerge when dealing with the details of the request for authorisation.

To address this situation, various options have been considered:

1.1. Single submission with separate assessment

One option would be for the sponsor to send the necessary documentation to all Member States concerned through a single 'EU portal' ('single submission'), administered by the European Medicines Agency ('the Agency'). The 'EU portal' would subsequently distribute the information to the Member States concerned.

Subsequent applications by the same sponsor (or, in certain cases, other sponsors) for authorisation of a clinical trial could simply refer to information previously submitted to the EU portal.
Preliminary appraisal: A single submission would greatly reduce the administrative work of sponsors for submission of documentation to the Member States concerned.

Consultation item no. 1: Do you agree with this appraisal? Please comment.

Item no. 1: YES, but this would only decrease the administrative burden and insufficiently address the problem. The CTA evaluation could be somewhat accelerated in the EU, but the separate assessment will end up with different queries and results.

Regarding the *assessment* of the information, this assessment would be done independently by each Member State, as at present.
Preliminary appraisal: A separate assessment would insufficiently address the issue set out above: The difficulties created by independent assessments would remain.

Consultation item no. 2: Do you agree with this appraisal? Please comment.

Item no. 2: YES, if the centralized procedure is followed by separate assessments, the process of CTA evaluation will not be significantly improved.

1.2. Single submission with subsequent central assessment

This option would be a single submission (see above), after which the submitted information would be centrally assessed by a scientific committee made up of representatives of all the Member States. This option, would be similar to the 'centralised marketing authorisation' for medicinal products.
Preliminary appraisal: A central assessment is not appropriate for clinical trials approval and would, as regards clinical trials, not be workable in practice for the following reasons:

- This option would insufficiently take account of ethical, national, and local perspectives. For these aspects, a parallel, national, procedure would have to be established in any case.
- The sheer number of multinational clinical trials per year (approx. 1200) would make centralised assessment very difficult. To this would add all substantial amendments of the clinical trials.
- The involvement of all Member State is not needed, as very few clinical trials are rolled out in more than five or six Member States.

Moreover, a Committee structure requires frequent meetings with a robust supporting infrastructure. The costs (and, consequently, fees) involved would make this mechanism unattractive for academic researchers.

Consultation item no. 3: Do you agree with this appraisal? Please comment.

Item no. 3: the appraisal is very realistic. Centralized assessment will certainly be expensive in terms of resources needed and unattractive not only for academic researchers, but also for industry. The differences in ethical issues among the different EU members could determine longer evaluation procedures.

1.3. Single submission with a subsequent 'coordinated assessment procedure'
This option would be a single submission (see above), which would be followed by a 'coordinated assessment procedure' (CAP). The CAP would be modelled, in some respects, on the decentralised procedure for marketing authorisations, while having a stronger element of joint assessment by the
Member States concerned.
The CAP would:

- allow all Member States concerned to input to the assessment of the application for a clinical trial regarding the aspects set out below (see point 1.3.1);
- provide for a 'Reporting Member State' whose role would be to lead the assessment of the application for a clinical trial;
- involve only the Member States concerned4 with a limited role for the Commission or the Agency – the latter acting as secretariat;
- only address certain aspects of the assessment of an application for a clinical trial (see point 1.3.1);
- lead to a 'single decision' per Member State which would include the aspects assessed in the CAP, as well as the ethical/local aspects of a clinical trial assessment (see point 1.3.1).

The CAP would apply to the initial authorisation of a clinical trial, as well as subsequent 'substantial amendments'.
Under the CAP, it would be up to each Member State to divide the tasks between the competent national authority and the Ethics Committee.
Preliminary appraisal: The CAP could offer a sufficiently flexible approach. It allows for a joint assessment without a cumbersome committee structure. It would allow national practice to be taken into account. It would respect that, as a basic rule, ethical issues clearly fall within the ambit of Member States.
Regarding the CAP, four issues need to be considered in particular and shall be discussed in this concept paper:

- Scope of the CAP (point 1.3.1);
- Disagreement with assessment report (point 1.3.2);
- Mandatory/optional use (point 1.3.3);
- Timelines (point 1.3.4).

1.3.1. Scope of the CAP

Not all aspects considered in a clinical trial application are suitable for an assessment in the CAP. In particular, ethical issues clearly fall within the ambit of Member States and should remain there.

To establish the scope of the CAP one has to have clarity of the three areas which are considered in a clinical trials application:

a) The risk-benefit assessment, as well as aspects related to quality of the medicines and their labelling. This includes the following:

- Acceptability of the clinical trial in view of all anticipated benefits, compared to risks and inconveniences for trial subjects (including control groups), taking account of
  - the characteristics of and knowledge about the investigational medicinal product,
  - the characteristics of the intervention compared to normal clinical practice;
  - the design of the trial;
  - the relevance of the trial, including the credibility of the results;
- compliance with the requirements for manufacturing and importation of the medicinal products intended for the clinical trial;
- compliance with the requirements for labelling of the medicinal products intended for the clinical trial;
- completeness and adequateness of the investigator's brochure.

b) Ethical aspects related to informed consent, recruitment and reward. This includes the following:

- completeness and adequateness of the information submitted to obtain informed consent;
- arrangements for rewarding and compensation of investigators and trial subjects;
- arrangements for the recruitment of trial subjects.

c) Local aspects related to suitability of sites, the investigator, and national rules. This includes the following:

- suitability of the investigator;
  - suitability of the clinical trials site;
  - adequateness and completeness of the insurance or indemnisation covering the investigator and sponsor;
  - compliance with the applicable rules on personal data protection.

Only the aspect under point a) would be suitable for the CAP. In particular, the aspects under b) and c) are not suitable for the CAP as they relate to ethical issues (as is the case for b) or to local expertise (as is the case for c).

Consultation item no. 4: Is the above catalogue complete?

Item no. 4: Yes, the list appears to be complete; perhaps more details are needed under "trial design" and number of subjects to be enrolled.

Consultation item no. 5: Do you agree to include the aspects under a), and only these aspects, in the scope of the CAP?

Item no. 5: Yes, we fully agree.

1.3.2. Disagreement with the assessment report

Disagreements amongst Member States about the assessment done under the CAP (ie the aspects listed in point 1.3.1.a) could be resolved in the following ways:

- an individual Member State could be allowed an 'opt out', if justified on the basis of a 'serious risk to public health or safety of the participant';
- the Member States concerned could vote on the issue and decide by simple

majority; or

- the matter could be referred to the Commission or the Agency for a decision at EU level.

Consultation item no. 6: Which of these approaches is preferable? Please give your reasons.

Item no. 6: the first approach is preferable, because any judgement that there is a "serious risk to public health or safety of the participant" should not be mitigated by the 2nd or 3rd approach.

1.3.3. Mandatory/optional use

As to whether the CAP should be mandatory or optional, three possibilities could be considered:

- CAP is **mandatory for all** clinical trials. (This would mean that the

provisions on authorisation in the Clinical Trials Directive would be replaced);

- CAP is **mandatory for all multinational** clinical trials. (This would mean that the provisions on authorisation in the Clinical Trials Directive would be maintained only for single-country clinical trials); or
- CAP is **optional**. (This would mean that sponsors could continue to refer to the national procedures laid down in the Clinical Trials Directive).

Consultation item no. 7: Which of these three approaches is preferable? Please give your reasons.

Item no. 7: the 2nd approach, because this is the type of trial for which there is a valid rationale for CAP. For its nature, CAP should be considered a harmonized assessment procedure among different EU members, aimed at evaluating a study protocol that should ensure coordination among member states in terms of planning, conducting the research and harvesting data.

1.3.4. Tacit approval and timelines

As a general rule the Clinical Trials Directive provides for a tacit approval by the national competent authority if, within 60 days, no grounds for nonacceptance have been raised.
In practice, a tacit approval is the exception. Moreover, this rule does not apply to Ethics Committees.
To take account of this, the CAP could be based on the concept of an obligatory single authorisation per Member State prior to commencement of the clinical trial. Under the CAP, a 'tacit approval' would not be possible.
Regarding timelines of the CAP, these should not be longer than the timelines provided today in the Clinical Trials Directive (i.e. as a general rule 60 days).
There should be clear rules on the timelines for the approval of substantial amendments,9 taking into account that the assessment is limited to the aspects of the clinical trial which have been subject to a substantial amendment.
Moreover, the timelines could be shortened where the risk to trial subjects is low and where the assessment in the CAP is limited largely to issues ofreliability of data. To this end, these types of trials (hereinafter 'type-A trials') could be identified in a pre-assessment.

A type A trial could be defined as '*a clinical trial which, on the basis of the following criteria, poses only minimal risks to the safety of the trial subject compared to normal clinical practice:*

(*a) The safety profile of all investigational medicinal products used in the trial is sufficiently known. This shall be the case if the investigational medicinal products used in the trial are:*

- *either authorised in a Member State concerned in accordance with Directive 2001/83/EC or Regulation 726/2004, and used within the authorised indication; or*
- *part of a standard treatment in a Member State concerned.*

(b) The interventions in the trial do not pose more than insignificant additional risk to the safety of the trial subject compared to normal clinical practice in a Member State concerned.'

Consultation item no. 8: Do you think such a pre-assessment is workable in practice? Please comment.

Item no. 8: the pre-assessment procedure could be workable in practice, but an efficient selection of studies is required. We suggest assessing a random sample of 100 RCTs to verify applicability of the criteria and percentage of type-A trials.

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

Various procedural aspects of EU regulation on clinical trials are not addressed in much detail in the legislation or fail to take into account practical limitations and requirements. This has led to a situation where Member States have slightly divergent national provisions based on identical concepts.
Often these differences are the result of Member States trying to align national requirements to the risk of a clinical trial in terms of trial subject safety or data reliability. However, if provisions diverge across the Union, the harmonising effects of the Clinical Trials Directive get lost.
National differences make multinational clinical trials more burdensome and expensive. This has a negative impact on clinical research – in particular in low prevalence conditions, such as rare diseases, where clinical trials have to be rolled out over many Member States in order to achieve robust results.
Moreover, these differences make it difficult for a sponsor to take 'responsibility' (see point 2.5) for the conduct of a trial which is partly performed in another Member State.
To address this, the following options have been considered:

2.1. Limiting the scope of the Clinical Trials Directive

2.1.1. Enlarging the definition of 'non-interventional' trials
The definition of a 'non-interventional trial' (Article 2(c) of the Clinical Trials Directive10) could be broadened, thereby excluding more studies from the scope of the Clinical Trials Directive (Article
1(1)).
At present, a 'non-interventional trial' is defined very narrowly. Three criteria have to be met simultaneously: the medicine is used within the terms of the marketing authorisation, there is no protocol and no additional intervention.
While some aspects of certain types of non-interventional trials have recently been harmonised at EU level,11 other aspects, as well as certain other non-interventional trials are still regulated at national level. Therefore, in some respects the rules for non-interventional trials may be in some Member States more lenient compared to those for clinical trials.
One may therefore argue that broadening the definition of a 'noninterventional trial' would limit the impact of the Clinical Trials Directive.
However, excluding trials from the scope of the Directive would also undermine past and future efforts to harmonise them to the extent that responsibility for regulating them would revert to

the Member States. This would introduce differences in trial subject protection in the EU. Moreover, it would make conduct of these studies in the EU more cumbersome.
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. 9: Do you agree with this appraisal? Please comment.

Item no. 9: YES, the aim of a harmonized procedure for CAP should reflect the need to include the highest number of studies within the boundaries of the Clinical Trials Directive. On the other hand, more efforts are needed to make the definition of "non-interventional trials" less open to interpretation, with specific regard to the most common methodologies used for observational studies, which should be encouraged.

2.1.2. Excluding clinical trials by 'academic/non-commercial sponsors' from the scope of the Clinical Trials Directive
It is not desirable to exempt 'academic/non-commercial sponsors' *as such* from regulatory requirements: It is difficult to see why rulesdesigned to protect the safety and rights of participants and thereliability and robustness of data should apply to some types ofsponsor and not to others. Besides, it is difficult in practice toestablish whether a sponsor is acting in a 'non-commercial' or a
'commercial' context. The commercial use of clinical trial data may be indirect, or may become apparent only after a clinical trial has ended. A number of other arguments in support of this view were put forward during the 2009/10 public consultation and listed in the summary of responses.
Moreover, if clinical trials by 'academic/non-commercial sponsors' were excluded from the scope of the Clinical Trials Directive, they would not be subject to harmonised rules at EU level. Member States would again be responsible for regulating these trials via national laws. This would introduce differences in trial subject protection in the EU. Moreover, it would make conduct of these studies in the EU more cumbersome, which is not in the interest of 'academic/noncommercial sponsors' performing clinical trials in different Member States.
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. 10: Do you agree with this appraisal? Please comment.

Item no. 10: YES, the Clinical Trials Directive should consider also academic / non-commercial sponsors. If the general aim of the present public consultation is to draw and plan a directive that could apply to multinational studies (whatever the sponsor, the drug, the enrolled subjects, etc), then the basic criteria should be very general, encompassing both commercial and academic sponsors.

2.2. More precise and risk-adapted rules for the content of the application dossier and for safety reporting
Often cited as examples for the need for greater harmonisation and risk adaptation in the European Union are the rules on

- the content of the clinical trials application dossier, and
- safety reporting.

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;
- he risk to data reliability and robustness;
- international harmonisation work, such as the guidelines of the International Conference on Harmonisation ('ICH').

The contents of the Annexes would build on work recently carried out by the Commission, in particular the *Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal*
product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1)12*13*, as well as parts of the *Detailedguidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinalproducts for human use* (CT-2), and the *Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use* (CT-3), which is currently underreview.
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.

Consultation item no. 11: Do you agree with this appraisal? Please comment.

Item no. 11: YES, especially for the third aspect. Please note that in Italy a decree is already in force on "detailed guidance on the request to the competent authorities and to the Ethics Committee for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial" (Ministerial Decree 21st December 2007).

Consultation item no. 12: Are there other key aspects on which more detailed rules are needed?

Item no. 12: No, we do not have further suggestions.

2.3. Clarifying the definition of 'investigational medicinal product' and establishing rules for 'auxiliary medicinal products'
Medicinal products intended for research and development trials are excluded from the rules for medicinal products as set out in Directive 2001/83/EC (Article 3(3) of Directive 2001/83/EC).
Some of these products fall within the definition of a 'investigational medicinal product' ('IMP') as defined in the Clinical Trials Directive (Article 2(c)). For these products, an extensive set of rules covers manufacturing, labelling, and even costs. These rules are often perceived as not risk-adapted and too onerous.
In practice, apart from IMPs a clinical trial involves often products which fall within the exemption of Article 3(3) of Directive 2001/83/EC, while not falling within the definition of IMP. Examples are medicinal products used as challenge agents, rescue medication, and background treatment. These medicinal products, which are often referred to as 'non-IMPs', are not specifically regulated in the Clinical Trials Directive.
In practice, the legal uncertainties surrounding these aspects, and the diverging approaches in Member States, create major difficulties when performing multinational clinical trials. To address this, the following cumulative approach could be pursued:

- 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';
- 'Auxiliary medicinal products' could be subjected to a proportionate regulatory regime, which would be separate from IMPs; and
- The rules for dossier requirements, reporting, and labelling for both IMPs and auxiliary medicinal products could be set out in the Annex to the basic legal act (see point 2.2).

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.

Consultation item no. 13: Do you agree with this appraisal? Please comment.

Item no. 13: Yes, the appraisal is justified and we agree.

2.4. Insurance/indemnisation

2.4.1. The issue
According to the Clinical Trials Directive, the liability of the investigator or sponsor for possible injury or death of the trial subject has to be covered by insurance or indemnity.
This general rule does not take into account, however, that clinical trials have very different risk-profiles. The actual risk of a clinical trial for the safety of a participant in that trial depends on a wide range of factors, and in particular:

- The extent of knowledge and prior experience with the IMP (in particular whether or not the IMP is already authorised in the EU or elsewhere);
- The intervention (which can range from a simple blood sample to a sophisticated biopsy) compared to normal clinical practice; and
- The subject population involved.

Thus, the risk for a trial subject varies considerably depending on the actual circumstances of the clinical trial.
The insurance requirements are a good example of where the Clinical Trials Directive does not sufficiently discriminate between degrees of risk. This has led to additional costs in two respects:

- costs for insurance; and
- costs for finding out about the insurance amounts needed.

2.4.2. Policy options
In order to address this situation, several policy options could be considered, such as:

- 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.

Preliminary appraisal: Both policy options could be a viable solution.

Consultation item no. 14: Which policy option is favourable in view of legal and practical obstacles? What other options could be considered?

Item no. 14: the removal of insurance for low-risk studies should not be pursued. Even if the risk is low, subject should be protected. The second option could be a more reasonable

approach and seems preferable especially for non-profit studies. A third option could be represented by grading the risk: this classification could help in solving the problem of defining a risk profile for the study, but this would probably require long preliminary work and not be feasible because of different perceptions of risk. We found it useful to consider the paper by Rid et al. on *"Evaluating the Risks of Clinical Reasearch"* (JAMA 2010; 304: 1472-1479), which provides a framework to minimise the influence of cognitive biases on the evaluation of research risks.

2.5. Single sponsor

The Clinical Trials Directive is based on the concept of a 'single sponsor' per trial. The single sponsor is 'responsible' for the trial vis-à-vis the national competent authority and the Ethics Committee.

It is a recurrent criticism that the concept of a 'single sponsor' renders multinational clinical trials more onerous.

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.

When assessing the possibility of 'multiple sponsorship'/'joint sponsorship'/'shared sponsorship'/'co-sponsorship', one has to bear in mind some important points:

- The responses to the 2009/10 public consultation show that the concept of 'responsibility' for the trial is often confused with 'liability' vis-à-vis the trial subject in case of damages. The latter, however, is a matter of civil/common law regarding contractual or extra-contractual obligations in the Member State concerned. When establishing the liability of a person or persons, the national rules for contractual and extra-contractual obligations apply. This issue is independent of the notion of 'sponsor' in the sense of 'responsibility vis-à-vis the national competent authority and the Ethics Committee'. Therefore, a concept of 'multiple sponsorship'/'joint sponsorship'/'shared sponsorship'/'co-sponsorship' would not allow an actor to evade liability in terms of civil/common law.
- Regarding the 'responsibility' of the sponsor, the main problem seems to stem from the divergent requirements amongst Member States for conducting clinical trials. If these requirements were truly harmonised (see point 2.2), the question of the 'responsibility' for a clinical trial may be less critical.
- No matter which of the above options is pursued, there has to be a person who can ultimately and authoritatively inform the national competent authority about the clinical trial, in particular in the case of multinational trials. Examples are information about status of a trial or about adverse reactions observed during the trial. This would have to be put down in agreements between the sponsors which would have to be verified by

national competent authorities or Ethics Committees.

Preliminary appraisal: In view of the above, option 1 may be preferable, 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. 15: Do you agree with this appraisal? Please comment

Item no. 15: YES. Option 1 is preferable.

2.6. Emergency clinical trials

This issue has been extensively explored in the 2009/10 public consultation (section 6) and discussed by stakeholders in their responses.
In order to address the situation, the Clinical Trials Directive should take into account internationally agreed texts (Declaration of Helsinki of the World Medical Association, the Convention on Human rights and Biomedicine of the Council of Europe, and the Guidelines on Good Clinical Practice of the International Conference on Harmonisation, 'ICH'). All these texts explicitly address the issue of 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 following
conditions:

- The trial subject is not in a state to give informed consent;
- The physical or mental conditions 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.

In this case, the 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. The same holds for the supply of information to the trial subject.
All other rules for clinical trials (approval, safety reporting, etc.) would remain applicable.
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.

Consultation item no. 16: Do you agree with this appraisal? Please comment.

Item no. 16: YES. Emergency clinical trials represent a critical area of research. This appraisal could be a first tentative step towards regulation of this type of clinical trials. From an ethical point of view, only when informed consent has been signed the patient may be enrolled, but in emergency this is not always possible (for example, it is difficult to enroll a sufficient number of patients during the first hours of their hospitalization in ICU). Furthermore, the situation *"The trial subject has not previously expressed objections known to the investigator"* should probably be reconsidered, because a procedure enrolling simply on the basis of the lack of patient's will seems hardly acceptable.

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

This issue has been extensively addressed in the 2009/10 public consultation (section 7) and discussed by stakeholders in their responses.
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.

Regarding the authorisation process for a clinical trial, this is currently addressed in point 2.7.2.4. of the detailed guidance CT-1, 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.*'
The Agency is currently assessing various actions in relation to the implementation of this provision.
Both provisions, as well as implementation work could be further supported and supplemented through the following:

- Codifying, in the revised legislative framework, 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 regulatoryframework 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*.

Consultation item no. 17: Do you agree with this appraisal? Please comment.

Item no. 17: YES, the appraisal is correct. This is a very important aspect. We have no further comments.

4. FIGURES AND DATA
The concepts discussed above are based on the figures collected by DG SANCO during the impact assessment exercise. These figures are annexed to this paper. It is crucial that these figures are checked and complemented by stakeholders where possible and necessary.

Consultation item no. 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.

Item no. 18: No, we have no further comments.