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Inserm

Institut national
de la santé et de la recherche médicale

Institut National de la Santé et de la Recherche Médicale

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

CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

The French National Institute of Health and Medical Research (Inserm) is a public scientific and technological institute which operates under the joint authority of the French Ministry of Health and French Ministry of Research. As the only French public research institute to focus entirely on human health, Inserm supports the development of research infrastructures in the field of public health and clinical research, particularly large health studies and clinical investigation centers; this implies fostering translational approaches and encouraging teams of different disciplines to unite around these infrastructures. These infrastructures have now matured, expanded their activity, and form a nationwide network that is listed on the national roadmap for research infrastructures and represents the national component of the ESFRI-roadmap infrastructure for clinical research (ECRIN), whose coordination is hosted by France.

In addition to its role in structuring clinical research in France, Inserm has set up a partnership and dialogue policy with associations for patients, the disabled and their families, based on four major initiatives: participation of associations in running research programs, involvement of associations in clinical research, training aimed at increasing the ability of associations to dialogue and play a part, overseeing the associations' network with a view to fostering exchanges between the scientific community and associations.

Finally, Inserm has promoted 190 clinical research protocols during the past five years, 120 of which are ongoing. Our expertise spans a wide range of different type of clinical study in all medical fields and encompasses first in human, proof of concept, exploratory, gene and cell therapy, explanatory, linked to constitution of biobanks or cohorts, medical devices studies. To conduct our subset of European clinical trials, we have set up a strong collaboration with the European Clinical Research Infrastructure network also known as ECRIN.

The following document is the outcome of our experience as an institutional sponsor of diverse studies, as a sponsor implicated in societal issues and as a sponsor of multinational studies.

GENERAL COMMENT

We welcome the opportunity to give our opinion about the revision of the clinical trial directive, especially about the idea of coordinating the assessment of multinational studies, expanding the scope of the Directive as well as the introduction of the notion of risk-based assessment. If these modifications are achieved, this will be a major step in simplifying the conduct of clinical studies.

We feel however, that this paper is avoiding tackling the issues linked to harmonization of the procedures of assessment by ethical committees. It is difficult to conceive that European countries that perform ethical evaluation of FP7 research program would be unable to establish a 'coordinated' assessment of clinical trials with all voices being expressed.

Finally, we feel that there is a need for Guidelines on such studies as epidemiological study as well as psychological studies (for example in terms of privacy, intrusiveness, risks, etc…

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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 costs; 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' administered by the EMA. The 'EU portal' would subsequently distribute the information to the Member States concerned. Subsequent applications by the same sponsor for authorization of a clinical trial could simply 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 state concerned.

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

We definitely agree with this appraisal. A single submission, as far as it concerns multinational clinical trials, would avoid the actual tedious work of sending a similar set of administrative documents to all national competent authorities involved.

Comments and suggestions

- Submission should be made online, using a set of application forms harmonized throughout Europe.
- Identical procedures should apply for subsequent modifications of the protocol.
- In addition, we feel that single submission should be effective not only when submitting to national competent authorities but also to ethical committees – this would require to define a common set of additional documents and requirements, the 'EU portal' acting as the distributing mailbox.

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 remains.

Consultation item no. 2 Do you agree with this appraisal?
We definitely agree with this appraisal.
Independent assessments can hamper the feasibility of a clinical trial because of divergent assessments that may be difficult to reconcile in a unique protocol. Further, the timeline for approval of the research varies enormously between countries. A coordinated assessment would be of great advantage as far as the timeline is well defined.

Comments and suggestions
- The Clinical Trial Facilitation Group has set up a Voluntary Harmonised Procedure to help circumvent these obstacles. However, to obtain the obligatory single authorization per Member State prior to commencement of the clinical trial, approval by the VHP group has to be followed by subsequent and additional submissions to each National Competent Authority involved. Therefore, this coordinated assessment will lead to a definite improvement of the VHP if no subsequent submission to the National Competent Authorities is required.

1.2. Single submission with subsequent central assessment

This option would be a single submission, after which the submitted information would be centrally assessed by a scientific committee made up of representatives of all Member States. This option would be similar to the 'centralised marketing authorization' 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 would make centralized 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 State. Moreover, a Committee structure requires frequent meetings with a robust supporting infrastructure. The cost (and consequently, fees) involved would make this mechanism unattractive for academic researchers.

Consultation item no. 3 Do you agree with this appraisal?
We fear that a central assessment by a European agency would introduce considerable delays due to the number of clinical trials submitted each year. However, we welcome the idea of 'centralizing' in some ways the assessment procedure through a 'coordinated assessment procedure' as defined in 1.3. Such a procedure could find inspiration in the ongoing VHP.

Comment and suggestion

- Coordinating the assessment by a scientific committee as proposed in 1.3. is a great step. We suggest taking advantage of the expertise already present in each Member State, members of this scientific committee should be representative of the national medical agencies and/or committees.
- Interactions with the Committee should be meant as a dialogue, so as to avoid reciprocal misunderstandings
- Only Member States involved in the trial should be solicited so as to keep the procedure as fluid as possible.
- Finally, the scope of the CAP assessment should be as broad as possible to avoid subsequent application to National Competent Authorities.

1.3. Single submission with a subsequent 'coordinated assessment procedure'

This option would be a single submission, which would be followed by a 'coordinated assessment procedure' (CAP). The CAP would be modeled in some respects, on the decentralized procedure for marketing authorizations while having a stronger element of joint assessment by the Member States concerned. The CAP would - allow all Member States concerned to input the assessment of the application for a clinical trial regarding the aspects set out below, - provide for a 'reporting Member State' whose role would be to lead the assessment of the application for the clinical trial, - involve only the Member States concerned with a limited role for the Commission or the Agency, the latter acting as a secretariat, - only address certain aspects of the assessment of an application for a clinical trial, - lead to a single decision per Member States which would include the aspects assessed in the CAP, as well as the ethical/local aspects of a clinical trial assessment. The CAP would apply to the initial authorization of a clinical trial as well as subsequent 'substantial amendments'. Under the CAP, it would be up to each Member States to divide the tasks between the competent national authority and the Ethics Committee.
Preliminary appraisal : The CAP could offer 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 (1.3.1), - disagreement with assessment report (1.3.2), - mandatory/optional use (1.3.3), - timelines (1.3.4).

1.3.1. Scope of the CAP

Not all the 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 labeling. 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 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 labeling 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, *adequateness and completeness 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 aspects 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 or to local expertise.

Consultation n°4 Is the above catalogue complete?
We suggest adding a few items to catalogue A) such as
- methodology, statistical plan, selection of subjects
- treatment of subjects
- randomization procedures and unblinding
- supplying, and handling of medicinal product
- pharmacovigilance,
- etc…

Consultation n°5 Do you agree to include the aspects under A) and only these aspects, in the scope of the CAP ?
We would suggest broadening the scope of the CAP, by including aspects listed in A) as well as some aspects of B) and C).
- Biases would be detrimental for subsequent public health recommendations. As a matter of fact, one should question how well results of the research may be expanded or translated to another population? Therefore, we suggest to add to list A) aspects such as *type of subjects included (gender, size, ..), *recruitment procedures, *Rewards and compensations of investigators, *Rewards and compensations of trial subjects, currently under lists B) or C),
- Currently, concerning insurances of multinational trials, separate insurance policies should be taken for each country. We have observed very divergent practices among these insurance policies for which there is no strong rationale. As an example, there is no ethic rationale to have strongly divergent levels of capita insured per head between European countries. Therefore, in case of multi national trials, we are in favor to include in the Directive the need for a unique insurance policy per multinational trial. In this case, it would be relevant to include this aspect in the scope of the CAP

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.
We are in favour of the 'opt out' option. We fear that simple majority option will be extremely criticised by the countries that are opposed to the trial and that referral for a decision at the EU level will delay further the commencement of the trial.

Comment and suggestion

- However, an 'opt out' decision by a State Member should only be possible if it this State member has strong reservations about risk to public health or safety of the participants which have not been answered after a dialogue has been set up with the sponsor. A detailed rationale should be transmitted to the sponsor.

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.
The best option would be to make CAP mandatory for all multinational trials. It would help harmonizing the procedures and make the whole process fluid.
We feel that trials rolled out in a unique State member should go through national procedures; this would require national procedures to be harmonised to the CAP procedure (scope of the assessment, role of NCA and EC).

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 of reliability 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?
Concerning the 'pre-assessment procedure', we agree, on principle, that preliminary identification of type A trial is workable. However, clear guidelines should be established and communicated on risk assessment.

Comment and suggestion

- pre-assessment procedures should be broadened to other type of studies (see 2.1.1)
- Concerning the timelines for obligatory single authorization per Member State, we agree with these being no longer than 60 days. However, one should make sure that requests for further information are sent in a timeline of 30 days to allow enough time to answers and revision of the documents.
  Similar constraints should apply to substantial amendments.

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, 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.
We agree on principle with this appraisal. Harmonized and proportionate requirements should apply to all type of clinical studies, including medical devices, explanatory studies, studies linked to biobank …. We would appreciate having more information on the requirements before giving a definite agreement.

Comment and suggestion
- Controversies on some medications (Thelin® / sitaxentan, Actos® / piogliatazone, ….) have recently arisen. One should be cautious when different levels of requirements may apply on clinical trials. Clear guidelines should be established.
- In any case, the requirements in terms of methodology, subject recruitments should not be minored.

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 rules designed to protect the safety and rights of participants and the reliability and robustness of data should apply to some types of sponsor and not to others. Besides, it is difficult in practice to establish 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.

We agree with this appraisal; proportionate requirements should apply independently of the nature of the sponsor.

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**; ***the 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)1213, as well as parts of the Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products 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 under review.
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.

It is proposed that Annexes to the basic legal act would include detailed provision on rules for conducting clinical trial in the EU, and that these Annexes would be updated, when necessary by the Commission by means of delegated acts. Content on these annexes would build on established 'Detailed guidances applying to clinical trial'.
On principle, we are in favor of detailed guidance to homogenize practices in Europe, reducing local interpretations. Therefore, we agree that these topics should be included in Annexes to the basic legal act, providing a single, EU-wide, risk-adapted set of rules.

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

Key aspects on which more detailed rules are needed concerns mainly

- Detailed classification of risk based approach
- IMP vs non IMP definition

Other aspects could be considered and introduced in these Annexes :

- Biobank (rules for duration of conservation, subsequent research, pediatric samples, derivation of iPS etc…)
- Explanatory study (no statistics…)
- Medical devices,
- Data Steering Monitoring Board, blinded vs unblinded analysis, conflict of interests policies…

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.

We agree on principle with this appraisal. Issues remain on how it affects the trial in terms of product supply, accountability, trail… , all aspects for which auxiliary medicinal (AMP) product may still need some level of requirements.

We would appreciate having more details on these issues and on the proportionate regulatory regime applying to IMP vs AMP before giving a definite answer.

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: 1 **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 2 **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?
We agree that it is aberrantly expensive to have insurance policies covering multinational trial as compared to a single insurance policy covering a national trial with a similar protocol and enrolling a similar number of subjects in a unique country.
However, we feel that 'insurance/indemnisation' policies should be mandatory for all trials (see consultation item no 9).

The idea of reducing the budget of a trial by allowing indemnisation by Member States is welcome. However, we do not foresee how a Member State could be under an obligation to provide for an indemnisation of damages incurred during clinical trial promoted by a private sponsor. Except, if sponsors either private or public, may contribute to an 'indemnisation fund' (see below).

What other options could be considered?

Another option would be to create a 'european indemnisation fund' or 'national indemnisation funds', to which all sponsors would contribute, according to study risk and number of subjects. The burden on trial budget would be minimal as contributions would be low when dealing with low-risk studies (majority of the study). This would apply for 'national' as well as 'multinational' trials.

Comment

We would like to remind that concerning insurance policies, we have encountered very divergent practices. According to our understanding of our mission as a sponsor, we feel unethical to have divergent policies according to countries, especially concerning the capita per head.

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.

On principle, we agree on option 1. As long as the requirements for conducting clinical trials are homogenized, there is no need for allowing multiple/joint/co sponsorship.

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.

We agree with this appraisal. Clear guidelines should be established including upon withdrawal of consent by the patient, parents, or legal representatives.

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-1,14 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.'16 The Agency is currently assessing various actions in relation to the implementation of this provision.17 Both provisions, as well as implementation work could be further supported and supplemented through the following: ▯▯Codifying, in the revised legislative framework,18 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.19 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.20

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

We agree that requirements for clinical trials performed in third countries should be on principle as stringent as European trials. However, our experience as promotor of trials in third country is too limited.

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

NA