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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.[1] 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).[2]

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

[1] See page 23 here: http://ec.europa.eu/atwork/programmes/docs/cwp2011_annex_en.pdf.

[2] http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm.

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- 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 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’ ('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.

Administrative costs are defined as the costs incurred by enterprises, the voluntary sector, public authorities and citizens in meeting legal obligations to provide information on their action or production, either to public authorities or to private parties (cf. Commission impact assessment guidelines, Part III, page 46).

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.
The idea of single submission is highly appreciated.

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.
A single submission alone would not be sufficient to address the issue of diverging local assessments. A streamlined and coherent assessment would also be needed- the idea of streamlining/coordinating the assessment procedure is recommended.

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.
Although we agree that a harmonised central approach has several logistical problems and it may not possible to finance such an approach, it would be the best way to address the problem. We cannot see any ethical or other national differences, which cannot be addressed in a central committee which includes members from different states. Ethics are of over-riding importance and should not be subject to national interpretations.

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 concerned[4] 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'.[5]

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.

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[4] Specific rules would have to provide for the possibility of extending the clinical trial to additional Member States after the application has been submitted or the clinical trial has been authorised.

[5] Regarding timelines see section 1.3.4.

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;[6]
- compliance with the requirements for labelling of the medicinal products intended for the clinical trial;[7]
- – 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;

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[6] On the term 'investigational medicinal product', see point 2.3.

[7] On the term 'investigational medicinal product', see point 2.3.

adequateness and completeness of the insurance or indemnisation covering the investigator and sponsor;[8]

- 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?
Under a) disease risk has to be added. It makes a difference whether a trial is designed for a low risk disease or for a high risk disease which is rapidly fatal and requires action. If a disease has a mortality risk of more than 90% (like many leukemias and cancers) a trial with a treatment mortality of 20%, but a cure rate of 40% is acceptable (and is accepted by the patients). During the last 30 years treatment optimization studies (TOPS) successfully addressed this unmet medical need.

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

The procedure described here appears to be a suitable compromise. The tasks described under a) are correct.

However if tasks summarised in b) and c) remain completely under the decision of the local ethical review board, major problems of clinical trial application remain unchanged (see general remarks).

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 would suggest referring the topic to the commission or the agency. The option to ‚opt out' cannot be accepted because the issue that one member state thinks that a study is a risk for public health whereas others do not, is not acceptable. A simple majority decision is also not appropriate for this situation. The European authority has the duty to provide sponsors with a reasonable decision and therefore has to seek for a compromise.

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.
Things should be kept simple. If the CAP is a reasonable procedure, which can be finalised without prolonging the timelines, it should be mandatory for all multinational trials. To reduce workload of central authorities CAP should not be extended to national studies.

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? Please comment.

The approach to define low-risk trials type A is excellent. It would extremely help for the conduct of treatment optimisation trials.

We would support the definition of type A trials. However we would not support the statement that a drug has to be used 'within the authorised indication'. Nowadays authorisation if often very narrow and pharmaceutical companies do not seek for extension of authorisation e.g. for rare diseases. In order not to discriminate studies for rare diseases we would state 'within the authorised or a similar indication'.

Type A trials should also include all trials with other non-drug treatment approaches such as stem cell therapy or irradiation if carried as defined by current standard of care. Type A trials should also include all treatment optimisation trials which represent general strategies and not aim for approval of particular drugs.

In this type of trials also the pre-requisites for reliability of data should be defined differently compared to higher risk trials. In particular approaches for a risk-adapted monitoring procedure should be encouraged. Several authorities have the position that on-site monitoring should be performed in all types of trials and act accordingly during their inspections. However on-site monitoring is neither necessary nor manageable in large treatment optimisation trials with large patient and/or site numbers. The Directive should refer to

ICH/GCP were it is stated that monitoring must be adapted in individual studies.

The major question is, who should make the pre-assessment and which timelines would be defined. In principle it should work and would help to focus the workload of authorities on trials with higher risks.

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 lowprevalence 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 Directive[10]) 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.

[10] References to Articles refer to the Clinical Trials Directive, unless indicated otherwise.

[11] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use (OJ L 348, 31.12.2010, p. 74); (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF)

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 absolutely agree to the statements about the current situation in different European countries.

There are in principle two options:

Define low risk trials within the EU directive:

The regulatory requirements for this type of trials need then to be reduced considerably including submission dossier, monitoring, safety, authority fees and particularly IRB approval. If the reduction of requirements for all theses issues is not achieved, the situation of academic and independent trials will not change and the limitations for independent academic research will not be alleviated.

Extend the definition of non-interventional trials:

The definition should be extended anyway because the current definition limits any type of epidemiologic research. It is not clear why an epidemiologic study is not allowed to have a protocol describing the research and standard diagnostics and treatments. Such protocols, if written by expert groups, are extremely helpful to ensure the standard of care particularly in rare diseases.

The member states should at the same time be requested to limit the requirements for non-interventional trials to an absolute minimum e.g. data protection rules and one single IRB approval.

To maintain and extend the term of non-interventional trials would help epidemiologic research, registries and standard of care research. Also treatment optimisation trials testing treatment strategies including combinations of registered drugs, non-drug approaches, risk stratification etc. could be summarized as non-interventional. It should be made clear that these are no drug trials and therefore not within the field of central drug authorities. In this type of trials neither extensive GCP requirements, nor rules to demonstrate qualification of centres and investigators, nor on-site monitoring or patient insurance should be requested.

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 the appraisal that specific rules for non-commercial trials are difficult to define. Non- commercial or academic trials may range from phase I to phase IV trials and may also be conducted with non-authorised drugs.
Therefore we are in favour of a risk-adapted approach as mentioned in Consultation item 8. The position of a non-commercial sponsor is important however with respect to fees for authorities, fees for IRB and submission and safety procedures. Non-commercial sponsors should be free to opt out regarding certain expensive technical procedures e.g. electronic submission of SUSARs etc. They should also be offered reduced fees.

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 riskadaptation 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)[12][13], 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.
Agreed (see also consultation item 10).

Consultation item no. 12: Are there other key aspects on which more detailed rules are needed?
We absolutely agree with the risk-adapted approach to define clinical trials and the respective regulatory requirements. The relevant issues are covered with the exception of the following topics:

- Need to have a patient insurance in low risk trials
- Definition of an investigational medicinal product

In order appraise the approach details regarding the respective regulations have to be presented.

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12 OJ, C 82, 30.3.2010, p. 1.

13 In particular points 2.3 to 2.9 of that detailed guidance.

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.
In principle we support the suggestion to narrow the definition of ‚investigational medicinal products’. There are two points to consider:

- A new definition should not lead to additional regulations for auxiliary medicinal products
- The commission should consider that some clinical trials use non-medicinal product approaches or combinations.

In oncology studies often authorised products are used within the authorised indication or in a very similar indication but in various combinations. The aim of these trials is treatment optimisation. Often it is impossible to even define one ‚investigational medicinal product’ because the combination of different drugs including non-drug approaches is studied.

Therefore it should be possible not to have an ‚investigational medicinal product’ in a clinical trial and to have auxiliary medicinal products only. The regulation of these auxiliary medicinal

products should be limited to an absolute minimum e.g. mentioning the name of the products in the protocol.

It should be made clear that auxiliary medicinal products, although used in clinical trials, have to be paid by health care systems including the preparation of the drug in hospital pharmacies and the application to patients.

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.

<u>Preliminary appraisal</u>: 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?
We would favour option A to remove insurance requirements for low-risk trials. Option B would lead to lack of international harmonisation and delays. Furthermore if, by definition a clinical trial participation has a comparable risk as standard therapy, there is no need to have an additional insurance.

To avoid insurance in all low-risk trials would considerably reduce costs and administrative work of sponsors and investigators. Overall – as outlined in annex – the insurance practically never pays for damage.

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.

We would not support option 1. Although it is clarified that responsibility and liability are different things, there will most probably no total harmonisation of the regulatory framework e.g. including national IRB approval, insurance, health care system, contractual issues with participating centres etc.

Therefore the regulation should have the option to have in international trials co-sponsors for each participating country. These co-sponsors should take the responsibility for the respective country including the responsibility to report to the main sponsor who can still be approached by the authorities. The main sponsor has however in this case not the duty to check the conduct of the trial in the different participating countries e.g. by audits.

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.
Overall we agree. However the concept paper does not address one type of clinical trials, which became extremely difficult under the Clinical Trials Directive.
Studies in rare diseases
In rare diseases such as subtypes of leukaemias or other cancers often a large number of centres have to participate in a clinical trial. In some entities sufficient number of patients can only be recruited in multinational settings. Many centres have to be activated with all bureaucratic and regulatory procedures although never a patient is recruited. On the other hand these cancers always represent an emergency situation and in the best interest of the patient treatment has to be started quickly.

Urgently variable procedures for rapid activation of centres – as soon as a patient is identified - need to come into place. It should be possible to initiate a centre within 2-3 days including regulatory approval and IRB approval.

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,*

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[14] See point 2.2. [15] Point 8.

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.

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.

No additional comments

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[16] See also recital 16 of Regulation (EC) 726/2004.

[17] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000072.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800268ad&jsenabled=true

[18] See point 2.2 above.

[19] See for example the Union initiative 'European and Developing Countries Clinical Trials Partnership' (http://www.edctp.org/).

[20] http://eudrapharm.eu/eudrapharm/selectLanguage.do?NOCOOKIE=NOCOOKIE&NEW_SESSI ON=true

General Remarks:

- Patients´ aspects and unmet medical needs require consideration and have to be defined.
- Harmonise EC and NAC approval.
- Even if EC approval will be done at national level, clear rules have to be defined.
- Life threatening diseases need special rules: risk of treatment should be related to the risk of death.
- Regulation for off label use especially for cancer patients and children (many treatments are off label) have to be adapted.
- More stakeholder/patient involvement necessary.
- Clarification for post authorisation studies needed, more clarity in definitions (registries, non-interventional).
- Assessment procedures: cost reductions and simplification for academics needed.
- Regulation needed for adult patients who are not able to give consent.
- The need for simplified application forms.
- Harmonisation of ethics network urgently needed (*Information:* EC has launched a European ethics committee network).

Stakeholders are invited to comment on this consultation paper, and especially on the boxed text, by 13 May 2011 at the latest. Responses should be sent preferably by e-mail to sanco-pharmaceuticals@ec.europa.eu, or by post to Unit SANCO/C/8, BREY 10/114, BE-1049 Brussels.

When sending your comments and responses, you should state whether you are a stakeholder association or a private individual. If you represent an association, please indicate clearly what type of association this is (patient, sponsor, investigator, hospital, IMP manufacturer, insurance company, etc.). If you represent a company, please state whether it falls within the EU definition of a small and medium-sized enterprise (i.e. less than €50million annual turnover and fewer than 250 employees).

All comments and responses will be made publicly available on the 'Clinical Trials' website[21] once the consultation period is over. If you do not wish your contribution to be made public please indicate this clearly and specifically in the documentation you send us (i.e. not just in the covering letter or e-mail). In this case, only an indication of the contributor will be disclosed.

Professional organisations are invited to register in the Union's Register for Interest Representatives (http://ec.europa.eu/transparency/regrin/) set up as part of the European Transparency Initiative to provide the Commission and the public at large with information about the objectives, funding and structures of interest representatives.

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[21] http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm.

Annex — key figures[22]

1. NUMBER OF CLINICAL TRIALS IN THE EU

In the EU/EEA[23], approx. 4000-6000 clinical trials are performed each year (cf. table 1). This equals approx. 8000 – 10000 clinical trial applications ('CTA') (cf. table 2). Approx. 64% of clinical trials are sponsored by the pharmaceutical industry and 36 % by other actors, such as academics.[24]

	2007	**2008**	**2009**	**2010**
Number of clinical trials applied for in the EU	5 028	4 618	4 491	4 193

Table 1: Number of clinical trials applied for in the EU:

	2007	**2008**	**2009**
Number of clinical trial applications in the EU	9 948	10 071	8 672

Table 2: Number of clinical trial applications in the EU:

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[22] All figures related to number of clinical trials, clinical trial applications, and subjects are sourced from EudraCT.

[23] For the purpose of this document, all references to EU or EU Member States shall include the EEA or EEA contracting States, unless otherwise indicated.

[24] When looking at clinical trial applications, the share of ‘commercial’ sponsors is 80 % (one clinical trial can imply up to 27 clinical trial applications — depending on the number of Member States concerned).

2. Number of multinational settings of clinical trials (EU)

Approx. 25% of EU clinical trials are performed in more than one EU Member State (cf. table 3). This equals approx. 60% of all clinical trial applications in the Member States, and to approx. 70% of all trial subjects.

Table 3: Number of Member States concerned per clinical trial in the EU:

	6	3	3	7817
19	1	5	5	490
20	3	1	1	3415
21	2	1	1	
22	0	3	3	
23	1	3	3	
24	0	1	1	8

3.

	2007	**2008**	**2009**	
Total	**5028**	**4618**	**4491**	**Patients involved in**
No of MSs concerned _				
1	3860	3541	3558	108 485
2	229	364	238	31 515
3	183	158	179	28 124
4	147	134	112	2614
5	98	104	93	19 064
6	86	97	74	1765
7	79	61	55	11 809
8	59	60	50	12 757
9	52	43	39	11 117
10	40	35	18	12 372
11	30	25	24	12 828
12	30	30	16	10 232
13	18	14	11	16 333
14	20	13	9	10 591
15	10	13	4	2966
16	7	5	1	
17	3	4	4	6724

Number of clinical trials per trial phase

The distribution of the clinical trials amongst the clinical trial phases is set out in Table 4.

Table 4: Distribution of Phases I-IV in clinical trials:[25]

4. Number of clinical trial participants (EU and global)

Tables 5 and 6 show the number of planned trial participants in the EU, and the number of planned trial participants globally, where at least one trial site is in the EU.

Table 5: Number of planned clinical trial participants in the EU:

[25] Source: EudraCT.

	2007	**2008**	**2009**	**2010**
Phase I	1510	1549	1462	1383
Phase II	1519	1340	1364	1185
Phase III	1176	972	932	918
Phase IV	904	826	780	707

	2007	**2008**	**2009**	**2010**
	535 481	404 166	358 429	396 784

Table 6: Total number of clinical trial participants planned (for clinical trials with at least one clinical trial site in the EU):

	2007	2008	2009	2010
	1 018 622	774 447	663 607	866 155

5. Staff figures in national competent authorities

Available resources in 2007 in the Member States for the scientific evaluation of clinical trial applications and amendments: In average approx. 5.3 FTE per Member State, i.e. 142 FTE in the EU.[26]

Available resources in 2007 in the Member States for the administrative tasks of CTA and amendments: In average approx. 3.3 FTE per Member State, i.e. 90 FTE in the EU.[27]

It is estimated that the available resources in the Member States for assessing suspected unexpected serious adverse reactions (SUSARs), as well as annual safety reports (ASRs), is approx. 10 FTE in the EU.

6. Estimated time needed for sponsors to comply with administrative requirements ('administrative costs')

The below is an **estimation**, based on some stakeholder information, of the time needed to collect information regarding the current application procedures, putting papers and documents together, fill in forms, send them etc. ('administrative costs'[28]). This does not include the substantial work, such as developing the design of a clinical trial.

6.1. Initial submission

The time needed to collect information regarding the current application procedures, putting papers and documents together, fill in forms, send them, etc. (i.e. excluding preparation of study documents, the protocol, IMPD, investigator's brochure etc) takes up, on average, approx. 5 man-days, i.e. 40 man-hours per CTA.

6.2. Follow-up information

[26] 'Impact on Clinical Research of European Legislation ('ICREL'), p. 78.

[27] ICREL, p. 79.

[28] Administrative costs are defined as the costs incurred by enterprises, the voluntary sector, public authorities and citizens in meeting legal obligations to provide information on their action or production, either to public authorities or to private parties (Commission Impact assessment guidelines, Part III, page 46).

According to estimations by stakeholders, in approx. 80% of all multinational clinical trials more than one NCA requests one additional information or raises grounds for non-acceptance.

In approx. 80% of all multinational clinical trials which are not approved without additional exchange of information, the national feedback is divergent as regards

- requests for additional information; or

-grounds for non-acceptance.

The time needed to collect this additional information, fill in forms, send them etc. takes up, on average, approx. 2 man-days, i.e. 16 man-hours.

6.3. SUSAR reporting

5 700 SUSARS are reported in average per year per Member State (national competent authority), i.e. approx. 154000 SUSARs.[29]

The time needed to fill in forms, send them etc. takes up, on average, approx. 90 minutes per SUSAR and per Member State (national competent authority and Ethics Committee).

6.4. Substantial amendments

Every year, approx. 1000 substantial amendments are submitted in average per Member State, i.e. approx. 27000 SAs per year.[30]

The time needed to collect information regarding the current application procedures, putting papers and documents together, fill in forms, send them, etc. (i.e. excluding preparation of study documents, the protocol, IMPD, investigator's brochure etc) takes up, on average, approx. 10 man-hours.

6.5. Costs per man-hour One man-hour in the area of regulatory affairs in clinical trials is worth approx. €45.

7. Insurance

7.1. Administrative costs

The time needed to collect information regarding the current rules, putting papers and documents together, fill in forms, send them, etc., in order to comply with national insurance/indemnisation requirements, takes up in average approx. 2 manhours per CTA.

7.2. Costs of insurance

[29] ICREL, p. 81.

[30] ICREL, p. 74.

Estimation of costs of insurance per patient per annum for insurance in different Member States (in €):

	14.50
France	75.00
Germany	75.00
Italy	50.00
The Netherlands	23.00

7.3. Number of incidences/level of damages

There are very limited figures on incidences of damage claims. The figures presented below have been submitted by stakeholders and Member States for the purpose of the impact assessment of the Commission.

• In one Member State (with approx. 200<1000 clinical trial applications per year), over a period of 9 years 14 claims were granted. The total amount of compensation for these cases was €43000. The administrative cost for the insurers is approx. €38 000. The total costs for the policy are approx. €235000.

• The 'German KKS Netzwerk — Koordinierungszentren für klinische Studien' has reported three liability cases with minor damages in trials over a period of 10 years (1997-2007) involving more than 20 000 trial subjects.

• In Finland, the Finnish Patient Insurance Centre and the Finnish Pharmaceutical Insurance Pool, between 2005 and 2010, received 19 requests for compensation, of which 4 led to compensation payment. According to EudraCT, since the entry into force of the Clinical Trials Directive there have been 299059 trial subjects planned for enrolment in Finland.

• In Denmark, according to the Danish Patient Insurance System (DPIS), over a period of 10 years 27 claims for compensation have been accepted from patients taking part in clinical research projects. This amounted to a sum of approx. €550000. According to EudraCT, since the entry into force of the Clinical Trials Directive there have been 117450 trial subjects planned for enrolment in Denmark.

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