**Answer to**

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

by the **MeDALL** Consortium

Please find attached the answer to the "REVISION OF THE CLINICAL TRIALS DIRECTIVE 2001/20/EC, CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION" by the MeDALL Consortium. MeDALL-Mechanisms of the Development of ALLergy is a collaborative project supported by the European Union under the Health Cooperation Work Programme of the 7th Framework programme (grant agreement number 261357) [http://medall-fp7.eu/]. The MeDALL consortium encompasses 23 public and private institutions, including 3 European SMEs. It is coordinated by Institut National de la Santé et de la Recherche Médicale (France). Pr Jean Bousquet (CESP U1018 INSERM, Villejuif, France) is the project coordinator and Dr. Josep M. Anto, (Centre de Recerca en Epidemiologia Ambiental (CREAL), Barcelona, Spain) is in charge of the scientific coordination. MeDALL aims to generate novel knowledge on the mechanisms of initiation of allergy from early childhood to young adulthood, in order to propose early diagnosis, prevention and targets for therapy. A novel definition of phenotypes of allergic diseases and an integrative translational approach are needed to understand how a network of molecular and environmental factors can lead to complex allergic phenotypes.

Several Work packages deal with clinical research and are thus interested by the public consultation on the CONCEPT PAPERREVISION OF THE CLINICAL TRIALS DIRECTIVE 2001/20/EC. One work package led by Dr Anne Cambon-Thomsen, Inserm U 1027, Toulouse, France is dealing with bioethical aspects and more generally the ethical, legal and social aspects of the project. As part of this work a regular survey of public consultations of relevance for the project is performed. The present Consultation has been signalled, explained and circulated to all members of the project and contributions solicited. The draft answer has been prepared by Velizara Anastasova, jurist in Inserm U 1027, in collaboration with other members of the team, especially Aurelie Mahalatchimy and Emmanuelle Rial-Sebbag, jurists, under the supervision of Dr Anne Cambon-Thomsen, MD, research director. A discussion between persons interested was then organised and the attached answer circulated to all participants before submission.

The MeDALL consortium is grateful to the Commission to have been given the opportunity to contribute to this consultation.

Velizara Anastasova and Anne Cambon-Thomsen, on behalf of the MeDALL consortium.

# Revision of the « Clinical Trials Directive » 2001/20/EC Concept Paper submitted for Public consultation

This public consultation includes 18 questions concerning the organisation of multinational clinical trials. These mainly concern the following areas:

- Cooperation in assessing and following up applications for clinical trials
- Better adaptation to practical requirements and a more harmonized, risk-adapted approach to the procedural aspects of clinical trials
- Ensuring compliance with Good Clinical Practices in clinical trials performed in third countries

The public consultation aims to investigate different options to improve the functioning of the Clinical Trials Directive. It attempts to remedy shortcomings and unintended negative consequences, whilst taking the global dimension of clinical trials into account and keeping the European clinical trial environment competitive. All these aspects will be reviewed by the Commission in its proposal when revising the Clinical Trials Directive in 2012.

## 1. Cooperation in assessing and following up applications for clinical trials

The Clinical Trials Directive provides common rules for the authorisation and regulatory follow-up of a clinical trial but does not lay down a mechanism whereby the application for the clinical trial is submitted jointly to all Member States concerned ("single submission"). Thus, the request for authorisation for a clinical trial is assessed independently by the various Member States concerned. This scheme raises two problems: first, identical information has to be sent to different Member States, which creates unnecessary administrative costs, and second the requirements set out in the Clinical Trials Directive are applied differently in the different Member States causing the emergence of divergent and conflicting points of view when dealing with the details of the request.

### 1.1 Single submission with separate assessment

In this context, the Commission proposes the implementation of the "single submission" system. The sponsor will send the necessary documentation to all Member States concerned through a single "EU portal", administered by the European Medicines Agency. The "EU portal" would subsequently distribute the information to all Member States concerned. Thus, the administrative work for the sponsor will decrease considerably.
**The assessment of information would be done independently by each Member State, as at present.**

**Item n°1: Do you think as the European Commission (EC) a 'single submission' would greatly reduce the administrative work of sponsors for submission of documentation to the Member States concerned?**

*Our opinion:* We agree with the opinion of the EC that single submission will reduce the administrative work and clarified procedure for the sponsor.

**Item n°2: Do you think as the EC a separate assessment would insufficiently address the issue set out above** (The difficulties created by independent assessments would remain)**?**

*Our opinion*: We agree with the opinion of the EC. The assessment would be done independently by each Member State, as it has been performed up to now. As a result, the inconvenience created by independent assessments would remain. A solution a minima could be to establish a common template for assessment such as a general checking list available for sponsors and interested parties at large and based on the requirements provided by existing guidelines.

### 1.2 Single submission with subsequent central assessment

This option would involve a single submission, after which the submitted information would be centrally assessed by a scientific committee of representatives of all the Member States. This option would be similar to the 'centralized marketing authorisation' for medicinal products.

**Item 3: What do you think about the proposal of a Single submission with subsequent central assessment**?

*The policy option of EC*: This kind of assessment is not appropriate for clinical trials approval and would, as regards clinical trials, not be workable in practice for several reasons such as:

- this option would insufficiently take account of ethical, national, and local perspectives;
- the sheer number of multinational clinical trials per year would make centralized assessment very difficult ;
- the involvement of all Member States is not needed, as very few clinical trials are rolled out in more than five or six Member States;
- the committee's structure would require frequent meetings with a strong and supportive infrastructure involved, which would render this mechanism unattractive for academic researchers;

*Our opinion:* We support the opinion of the EC for the same reasons mentioned above, apart that the frequent meetings aspect is not only unattractive for academic researchers, but unattractive for everybody. There is no reason to make a case for academic researchers only here.

### 1.3 Single submission with a subsequent «coordinated assessment procedure » (CAP)

This option would entail a single submission which would be followed by a "coordinated assessment procedure" (CAP). The CAP would be patterned, in some aspects, on the decentralized procedure for marketing authorisations with a stronger element of joint assessment by the Member States concerned. The CAP would allow all Member States that are involved to participate in the assessment of the application for a clinical trial for some part. A Reporting Member State shall be appointed to lead the assessment of the application. The CAP would lead to a single decision per Member State which would include the aspects assessed in the CAP and the ethical/local aspects of a clinical trial assessment. The CAP would apply to the initial authorisation of a clinical trial, as well as subsequent substantial amendments.

*The policy option of EC:* 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.

*Our opinion:* This procedure seems appropriate to avoid the various problems faced by the sponsor. However, some observations appear useful:

- The modalities of coordination (scope, disagreement, timelines) of such an assessment procedure should be clearly delineated in the amended text of the Clinical Trials Directive;

- It should be documented which level of control is applied by each competent national authorities ; besides, it would be useful that information regarding the Ethics Committee mandate and rules of procedure is made available in an information base centrally available;

- Even though the role of the Agency would be limited to secretariat tasks, it should be emphasised the necessary need for Member States authorities to exchange information with the Agency particularly for Pediatric clinical trials.

#### 1.3.1 Scope of the CAP

To establish the scope of the CAP, one has to be aware 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:

- Acceptability of the clinical trial in view of all anticipated benefits, compared to risks and inconveniences for trial subjects;
- Compliance with the requirements for manufacturing and importation of the medicinal products intended for the clinical trial;

- Compliance with the requirements for labelling of the medicinal products intended for the clinical trial;
- Completeness and adequateness of the investigator's brochure;

b) Ethical aspects related to informed consent, recruitment and reward*:*

- 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 the suitability of sites, investigators and national rules. suitability of the investigator:

- Suitability of the clinical trials site;
- Adequateness and completeness of the insurance or indemnisation covering the investigator and the sponsor;
- Compliance with the applicable rules on personal data protection.

*The policy option of EC:* 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 are related to ethical issues (as is the case for b) or to local expertise (as is the case for c).

**Item n° 4: Is the above catalogue complete?**

*Our opinion*: We think that these three areas are sufficient to determine the scope of CAP. But, to complete the catalogue, compliance with rules on clinical trials shall be added even though it is implicit. Moreover, regarding ethical aspects, it shall also be added that international and European norms shall/must be respected (according to the legal value of the norm considered).

The fact that Member States would cooperate only on some aspects of the procedure is fairly appropriate, but more details to define them are needed.

**Item n° 5: Do you agree to include only the aspects concerning the risks / benefit assessment and the aspects related to quality of the medicines and their labelling in the scope of the CAP?**

*Our opinion*: We agree with the proposal of the Commission that aspects related to suitability of sites, the investigator, and national rules are not suitable for the scope of CAP as they relate to local expertise, and the relevant Member State is the best placed for this.

However it appears difficult to limit the scope of the CAP only to the aspects under a). For instance, it would be relevant for the CAP to assess the compliance with the relevant EU rules. Otherwise, the objectives of the creation of the CAP could be missed. Thus, it would be relevant to add under a), the compliance with the relevant EU rules, especially regarding clinical trials and specific disposals for minors, and personal data protection.

### 1.3.2 Disagreement with the assessment report

The EC proposed three different ways to resolve the disagreement between the Member States about the assessment done under the CAP:

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

**Item n°6: Which of these three approaches is preferable in the context of CAP? Please give your reasons.**

*Our opinion*: We consider that the first approach in which individual Member State could be allowed an "opt out" if justified on the basis of "serious risk to public health or safety of the participants" is the most appropriate in the context of CAP. It could be added that a Member state can also opt out on ethical grounds. This solution corresponds to the logic of coordination planned by CAP because it leaves some leeway to each Member State affected by the clinical trials. Moreover, public health protection of and participants' safety are the primary goals of the Clinical Trials Directive. If another mechanism would be chosen *in fine*, the mechanism of this decision should be mentioned in the information to participants.

### 1.3.3 Mandatory/optional use

**The EC suggests three possibilities:**

- CAP is mandatory for all clinical trials
- CAP is mandatory for all multinational clinical trials
- CAP is optional

**Item n°7: Which of these three approaches is preferable? Please give your reasons.**

*Our opinion***:** We believe that the second approach, which provides that CAP will be mandatory for all multinational clinical trials, is preferable. It seems that this policy option is the most appropriate to achieve the objectives of the revision of the Clinical Trials Directive in order to reduce the administrative work when submitting documentation to the Member States and to avoid conflicting points of view between Member States when dealing with the details of the request for authorisation. This option could enable competitiveness in the European clinical trials environment.

The CAP should also be mandatory for all medicinal products eligible for the centralised marketing authorisation such as orphan drugs and Advanced Therapy Medicinal Products.

### 1.1.1 Tacit approval and timelines

As a general rule, the Clinical Trials Directive provides a tacit approval by the national competent authority if, within 60 days, no grounds for a rejection have been raised. However, this rule does not apply to Ethics Committee and, in practice, a tacit approval is the exception. To take this into account, the CAP could be based on the concept of an obligatory single authorisation per Member State provided in a maximum of 60 days prior to commencing the clinical trial. Under the CAP, a 'tacit approval' would not be possible.
There should be clear rules on the timelines for the approval of substantial amendments, taking into account that the assessment is limited to the aspects of the clinical trials which have been subjected to a substantial amendment.
These timelines could be shortened where the risk for subjects of the trial is low and where the assessment in the CAP is largely limited to issues of reliability of data. 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 authorized in a Member State concerned in accordance with Directive 2001/83/EC or Regulation 726/2004, and used within the authorized 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.*"

**Item n°8: Do you think such pre-assessment is workable?**

*Our opinion*: We agree with EC on the proposed definition of type-A trials. Hence, the pre-assessment seems applicable in practice. The 60-days period for pre-assessment also seems appropriate. However, the 30 days-delay extension for regenerative medicine products qualifying as Advanced Therapy Medicinal Products shall be maintained as well as the extension by a further 90 days where the consultation of a group or a committee is deemed required.

## 2. Better adaptation to practical requirements and a more harmonized, risk-adapted approach to the procedural aspects of clinical trials

Various procedural aspects of the EU regulation on clinical trials are not addressed in sufficient 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. National differences have a negative impact on multinational clinical trials because they make them more burdensome and expensive. Moreover, these differences make it difficult for a sponsor to take "responsibility" for the conduct of a trial which is partly performed in another Member State.

### 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" could be broadened, thereby excluding more studies from the scope of the Clinical Trials Directive.
At present, a "non-interventional trial" is defined very narrowly[1]. Some aspects of certain types of non-interventional trials have recently been harmonized at the EU level, but other aspects, as well as certain other non-interventional trials are still regulated at a national level. Therefore, in some aspects the rules for non-interventional trials may be more lenient than those for clinical trials in some Member States. It could be argued that broadening the definition of a "non-interventional trial" could limit the impact of the Clinical Trials Directive.
Excluding trials from the scope of the Directive would also undermine past and future efforts to harmonize them to the extent that the responsibility for regulating them would revert to the Member States.

*Policy option of EC:* 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 harmonized and proportionate requirements which would apply to *all* clinical trials falling within the scope of the present Clinical Trials Directive.

**Item n° 9: Would it be more appropriate to broaden the definition of non-interventional trials which are excluded from the scope of the Clinical Trials Directive, or would it be better to come up with harmonized and proportionate requirements which would apply to all clinical trials including non-interventional trials?**

*Our opinion*: We approve the policy option proposed by EC for the same reasons as those mentioned above.

### Excluding clinical trials by "academic/non-commercial sponsors" from the scope of the Clinical trial 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 safety, rights of participants, 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. Moreover, if clinical trials by "academic/non-commercial sponsors" were excluded from the scope of the Clinical Trials Directive, they would not be subjected to harmonized rules at EU level and this would introduce differences in the protection of the clinical trial participant..

*Policy option of EC:* Rather than limiting the scope of the Clinical Trials Directive, it would be better to come up with harmonized and proportionate requirements for clinical trials. These

[1] The medicine is used within the terms of the marketing authorisation, there is no protocol nor additional intervention

proportionate requirements would apply independently of the nature of the sponsor – "commercial" or "academic/non-commercial".

**Item n° 10: Is it necessary to exclude clinical trials "academic/non-commercial sponsors" from the scope of the Clinical Trial Directive or would it be better to develop harmonized and proportionate requirements for clinical trials applicable independently of the nature of the sponsor?**

*Our opinion*: We approve the policy option proposed by EC for the same reasons mentioned above.

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

The rules on the content of the clinical trials application dossier and safety reporting are often quoted as examples of the need for greater harmonization and risk adjustment in the European Union.
To address this need, sufficiently detailed provisions on these topics could be included in Annexes[2] to the basic legal act and 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 of the participant in a trial in terms of safety compared to normal clinical practice;
- the risk for data reliability and robustness;
- international harmonization work, such as the guidelines of the International Conference on Harmonization ('ICH').

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

**Item n° 11: Does the establishment of one single, EU-wide, risk-adapted set of rules for the content of the application dossier and for safety reporting help simplify and streamline the rules for conducting clinical trials in the EU? Please comment.**

[2] The contents of the Annexes would build up 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.

*Our opinion*: We agree with the approach proposed by the EC. On the one hand, the establishment of such a single, EU-wide, risk-adapted set of rules would give a common basis for all Member States regarding clinical trials. On the other hand, this group of rules would be incorporated into the future Clinical Trials Directive meaning that they will have a greater legal value.
However, it should let the opportunity to complete this list of rules because it is impossible to anticipate all the risks that can emerge with future technologies.

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

We propose to establish EU-wide common criteria for the identification of risks in a non-binding text. Thus it would be possible to take into account the particularity of Paediatric clinical trials because they have a high level risk.

**Clarifying the definition of "investigational medicinal products" and established rules for "auxiliary medical 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.
Some of these products fall within the definition of an "investigational medicinal product" ("IMP") as defined in the Clinical Trials Directive. For the IMPs, an extensive set of rules covers different aspects (manufacturing, labelling and costs) but these rules are often perceived as not risk-adapted and too onerous.
In practice, apart from IMPs a clinical trial involves often products which do neither fall within the definition of IMP ("non-IMP") nor in the scope of the medicinal products Directive (Directive 2001/83/EC). These non-IMPs are not specifically regulated in the Clinical Trials Directive. Therefore, the legal uncertainties surrounding these aspects, and the diverging approaches in Member States, create several burdens when performing multinational clinical trials.
To resolve 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*[3]*, 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.

[3] Medicinal products intended for research and development trials

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

**Item n° 13: Does the narrowed definition of "investigational medicinal products" and establishement of rules for "auxiliary medicinal products" help to simplify, clarify and streamline the rules for medicinal products used in the context of a clinical trial?**

*Our opinion*: We approve the policy option of the EC. Indeed, a narrowed definition of "investigational medicinal products" and rules for "auxiliary medicinal products" would permit: on the one hand to fill the regulatory gap for non-IMPs and on the other hand to avoid the diverging national approaches and therefore remove several burdens when dealing with the authorisation application.

### 2.3 Insurance/indemnisation

#### 2.4.1 The issue

The general rule providing that the liability of the investigator or sponsor for possible injury or death of the trial subject has to be covered by insurance or indemnity does not take into account that clinical trials have very different risk-profiles. The actual risk of a clinical trial for the safety of a participant depends on a wide range of factors[4] which vary considerably depending on the actual circumstances of the clinical trial. However, the Clinical Trials Directive does not sufficiently differentiate between degrees of risk. This has led to additional costs in two aspects: costs for insurance and costs for finding out about the insurance amounts needed.

#### 2.4.2 Policy options

In this context, several policy options could be considered, such as:

- Removing insurance/indemnisation requirements for low-risk trials; or
- Optional indemnisation by Member State: these Member States would have an obligation to provide for an indemnisation for damages incurred during clinical trials performed in their territory, taking into account the national legal system for liability.

*Policy option of EC*: Both policy options could be a viable solution.

**Item n° 14: Which policy, removing insurance/indemnisation requirements for low-risk trials or optional indemnisation by Member States, is more favorable in view of the legal and practical obstacles? What other options could be considered?**

[4] Especially the extent of knowledge and prior experience with the IMP, the intervention compared to normal clinical practice and the subject population involved;

*Our opinion*: We think that the second policy option is more appropriate as it could be difficult to identify low-risk trials. As the EC stated, the actual risk of a clinical trial for the safety of a participant considerably depends on the actual circumstances of the clinical trial. Thus, the Member State directly concerned by the clinical trials would be more able to assess damages incurred during trials and to indemnify the participants in view of the actual context of clinical trial.

### 2.4 Single sponsor

The Clinical Trials Directive is based on the concept of a "single sponsor" per trial who 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. Thus, 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, some aspects should be taken account:

- 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 and 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 harmonized, the question of the 'responsibility' for a clinical trial could be less critical.
- No matter which of the above options is pursued, there needs 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. 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.

*Policy proposal of EC*: 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 harmonized.

**Item n° 15: Should the concept of "single sponsor" be kept or should the concept of 'multiple sponsorship'/'joint sponsorship'/'shared sponsorship'/'co-sponsorship regarding "responsibility" for the conduct of a trial which can be partly performed in another Member State be preferred?**

*Our opinion:* It appears clearer and easier to have a single responsible sponsor. However, we think that an intermediate option is more appropriate for multinational clinical trials. We deem that the concept of co-sponsorship could be preferable in the context of multinational clinical trials but all sponsors should designate one sponsor among them who takes responsibility in terms of responsibility towards the administration authorizing and controlling the trial. The distinction between responsibility vis-à-vis the national competent authority or Ethics Committees and civil law/common law liability should be made clear.

### 2.5 Emergency clinical trials

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'). In view of these texts, the Clinical Trials Directive could be amended so that the informed consent and the information from the investigator may take place during or after the clinical trial under the following conditions:

- The participant in the trial is not in a state to give informed consent;
- The physical or mental conditions that prevent giving informed consent are a necessary characteristics 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 (in case of minors)/legal representative (in case of adults) or from the participant in the trial, whichever is sooner. The same holds for the supply of information to the participant. All other rules for clinical trials (approval, safety reporting, etc.) would remain applicable.

*Policy proposal of EC*: 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.

**Item n° 16: Does this policy approach which is in line with international instruments relating to emergency clinical trials to regulate such situation seems appropriate? Please comment.**

*Our opinion*: We entirely approve the policy option proposed by the EC. Indeed, this approach seems logical because all mentioned texts constitute a common basis in this area and also are widely accepted and implemented in the Member States. However, we consider that

this set of texts should be completed by the Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research.

## 3. Ensuring compliance with Good clinical practices in clinical trials performed in third countries

The Commission is committed to ensure 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.

*Policy option of EC*: 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.

This objective is addressed in specific sections of applicable texts[5] the Annex of Directive 2001/83/EC[6] regarding the marketing authorisation process of medicines.
It could be further supported and supplemented through the following:

- Codifying, in the revised legislative framework, the provision in point 2.7.2.4. of the detailed guidance CT-1; and
- Further supporting capacity building in third countries where the regulatory framework for clinical trials, including its enforcement is weak.

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

[5] Point 2.7.2.4 of the detailed guidance CT-1 regarding the authorisation process for clinical trials: ""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."

[6] Point 8 of the introduction to the Annex of Directive 2001/83/EC[6] regarding the marketing authorisation process of medicines "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."

**Item 17: Does the requirements ensuring compliance with Good clinical practices in clinical trials performed in third countries shall be supplemented regarding capacity building in third countries? Shall we legally require clinical trials performed in third countries to be registered in the EU clinical trials database and published via the public EU-database to accept the results of these clinical trials in the context of a marketing authorisation process in the EU?**

*Our opinion*: We entirely approve the policy option of EC. However, two additional comments should be made:

- establish a list of supra national reference texts used by EC to ensure compliance with Good Clinical Practices ;

- all relevant texts should be set out in the Annex of the future amended Clinical Trials Directive;

Thus, third countries will have specific European requirements in this area and will refer to specific rules for compliance.

**Item 18: Do you have any comments or additional quantifiable information apart from that out in the annex to this document? If so, you are invited to submit them as part of this consultation exercise.**