Clinical Trials Facilitation Group
CTFG

28 April 2011

Comments of CTFG on the European Commission's concept paper regarding the revision of the « Clinical Trials Directive » 2001/20/EC

The Clinical Trials Facilitation Group, CTFG is a workinggroup of the Heads of Medicines Agencies (HMA), appreciates the Commission's initiative to propose practical options addressing some of the key issues of the clinical trials directive (CTD). CTFG is happy to have the opportunity to comment on those proposals and will focus mainly on the two first sections dedicated to cooperation in assessing clinical trials (CTs) and a risk-based adaptation of CTs processes.

1. Cooperation in assessing and following up CT applications (CTA) for clinical trials

The objectives of the CTD, which are to protect CT participants and to ensure the credibility of the CT results are reinforced by the Commission. Therefore the CTFG proposes to include those objectives in the title of the CTD.

The Commission introduced several options to set up cooperation in "assessing and following up applications for CTs". Those options, although not currently described in the CTD, have been voluntarily introduced by the member states (MS) themselves, at least at the national competent authorities (NCAs) level. The Heads of Medicines Agencies (HMA) have realised from the beginning that harmonisation between NCAs needs to be promoted with the aim to reduce the sponsors' workload, to ensure the same level of subjects protection and to avoid discrepancies between NCAs. For those reasons, the CTFG was created in 2004 as a network of the NCAs in charge of CT assessment and follow up.

Since 2004, CTFG has proposed different procedures to promote this harmonisation, among which the voluntary harmonisation procedure (VHP) for a coordinated assessment of multinational CTA (2008) and a pilot of an internal work-sharing of safety data assessment (2010). Those processes have been proposed and set up within the current legislation and this experience should be the basis for the revision.

Although the title of the section announces cooperation in "following up CT applications" , the Commission proposes only options to cooperate in assessing CTAs but there is no option addressing any responsibilities – process - assessing CT safety data (as SUSAR, DSUR, signalling): this important process should be included in the project. It could be taken up as a task by the CTFG .

Options proposed by the Commission to cooperate in CTA assessment deal with all the CTs (mono and multimember states CTs, approx. 75 and 25%, respectively).

- The proposals include a single submission of CTA, namely an electronic submission to all MS Concerned (MSC) through a single EU portal at EMA, including applications to NCAs and to national Ethics Committees (EC).

Commission's 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.

CTFG comments: CTFG endorses the principle of a single EU portal / one stop shop for CTs as it may be helpful for sponsors, reduce administrative burden and might facilitate the conduct of CTs in EU, at least for the multinational clinical trials.

The EU portal proposed by the Commission is supposed to be applied to all CTs in EU. It would distribute applications to the MSC, to NCAs and the EC concerned, assuming that each MS is able to receive them electronically and to forward them to NCAs and the EC concerned.

The feasibility of such a process needs to be closely evaluated as it is based on:
- the absence of any additional national specificity at the competent authority level and at the EC level, bearing in mind that documentation for ECs currently necessarily needs to contain a great part of country specific information and in local languages,
- the large number of national ethic committees supposed to receive dossiers
- the capacity of each MS to retrieve their CTA (receiving, validating, getting fees…),
- a feasible IT infrastructure (very high reliability, very high capacity).

A step-wise implementation should be proposed, starting with MNCTs for which a coordinated assessment is performed.
Furthermore, taking into account the need to introduce a portal rapidly, the Commission is invited to evaluate the most efficient and the low cost solution for the development and the location (at EMA level or at HMA/one NCA level).

In this context, technical and practical modalities should be more detailed, including:
- A harmonised format capable to handle NCAs and ECs requirements
- Evaluation if the IT solution might be taken care by responsibility of HMA
- Functionality of IT solution (including repository for internal documents) and its compatibity to MS IT
- Validation of the CTA administratively and of content, e.g. at submission gate and MSC, respectively.

- 3 options for CTA assessment

The assessment is proposed to be done
1) either by each MS concerned, as by: is the current situation
2) either centrally by a scientific committee with all the MS being represented, as in the marketing authorisation (MA) centralised procedure.
3) or through a coordinated assessment procedure by the MS concerned (so called the CAP).

1.1. Single submission with separate assessment

Commission's 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.

CTFG Comments: CTFG agrees that this system is not the most appropriate for the MNCTs. However, taking into account the fact that 75% of the CTs performed in EU are conducted in only one MS, the principle of a mononational assessment is to be maintained for CTs:

- either as the current situation (application submitted and assessed by that MS concerned),
- or CTA is submitted through an EU single portal and assessed nationally, if full IT functionality is given and sufficiently tested by multinational CTAs,
- or the CTA comes through the CAP (submission to the EU portal and then the CAP process/assessment is applied only by that MS) .

1.2. Single submission with subsequent central assessment

This option would permit an EU-wide CT authorisation similar to the current centralised procedure for MA, with one assessment by a multinational committee of all MS.

Commission's 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 rather 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 researches.

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

CTFG agrees with the Commission that the process proposed is not the most appropriate for CTs mainly because of ethical, national and local aspects of the trials, because of its lack of flexibility and reactivity, because of the unnecessary involvement of all MS when only 25% CTs are multinational and only around 10% of CTs concern more than 4 MS, and because it would require infrastructure and personnel at both the level of EMA and NCAs (since MS will still, be those who assess).

1.3. Single submission with subsequent "coordinated assessment process" (CAP)

CAP is a process that mixes up several (new) principles:

- Maintaining national decisions for CTAs
- Input of concerned MS in the assessment of CTs with a Reporting MS (RMS) to lead the assessment of multinational CTA,
- EMA's role as the secretariat of CAP
- Creation of a limited joint assessment by MSC on predefined aspects and a national assessment for other ethical and local perspectives

- A single national approval of the CT as a whole, including NCA and EC assessment and including aspects related to the defined joint assessment and the ethical/local aspects of CTA
- Definition of the scope of what should be assessed in cooperation by the MS concerned (joint assessment/section a) and what should be assessed nationally (ethical and local aspects/sections b and c)
- Involvement of MS as a whole including both NCAs and ECs in the process, without defining exactly the scope of each body (letting each MS organise the distribution of tasks).
- Time lines of 60 days for the single national decision.

Commission's 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.

CTFG Comments: CTFG strongly supports the principle of a coordinated assessment by the MS concerned as it has been set up within the VHP.
In details, each of the new principles proposed by the Commission needs to be discussed. Some of them are reviewed later in the document such as the scope of the CAP, or in case of disagreement with assessment report, mandatory/optional use and timelines.

The principle of maintaining the CT approval at the national level is also supported, allowing the MS to ensure their own responsibilities on CTs conducted in their territories.

The principle of a coordinated assessment with a RMS coordinating all the MSC assessment and building up one common position is endorsed, as it is currently set up in the VHP. However further details need to be discussed with the MS such as the provisions to nominate the RMS, detailed procedures and necessary resources including IT etc.

Once again, the CAP should benefit from the VHP experience among NCAs which has shown that harmonisation in assessment needs:
- NCAs to have a common scope of assessment and objectives
- NCAs to have the same general principles on CT assessment
- NCAs to have the same process (same dossier, simultaneous application, same time lines)
- NCAs to benefit from appropriate IT tools to accelerate reviews and share assessments, including a single electronic repository (as in the VHP process) and a data management system, including tracking system
- NCAs need to be flexible
- NCAs need to benefit from an administrative coordinator of the system
- NCAs assessment to be supported by a leading Member state per CT
- All NCAs to participate in the system at the same time.

One of the difficulties in the VHP is that in some countries, the already existing requirement of the single decision (NCA + EC) has increased the process timelines for the national approval dramatically.

The secretariat of CAP should be ensured by the HMA CTFG and not EMA due to the fact that only the MS are involved in CT decision. The VHP experience by the CTFG can be taken into account to build up this secretariat whereas EMA is responsible for maintaining the CT databases (EudraCT and EVCTM).

CTFG should have a formal mandate with a legal base as the body in charge of co-ordinating the CAP.

In such a context, the provision of the appropriate IT tools needed to be developed to assure the adequate support for the CAP (public and internal repositories; data management systems…) should be evaluated and detailed in the document.

The principle of a single national decision replacing the current system of 2 independent assessments by NCAs and ECs, deletes this crucial independence. Furthermore, in some MS this single decision system has been set up and is currently characterised by increased time-lines of the final single decision.
Furthermore, this system would force ECs to reorganise their own process in order to be able to give a final opinion within 60 days, meaning the possibility to use a clock stop will be diminished. Such an organisation might be an issue since ECs use to work through regular (generally monthly) meetings as a voluntary basis and not as time-full jobs.
To conclude, CTFG is in favour of maintaining independent NCAs and ECs assessments, although the CTFG recognises the need to further develop respective exchanges of information. The roles/responsibilities and communication between the 2 bodies could be further detailed in the legislation and not mixed up with the CAP process.

Taking that into account, CTFG supports the idea of a legal coordinated joint assessment by the MS concerned but is convinced that it should be performed generally by NCAs only and within a detailed process of coordination by CTFG with appropriate IT tools.

The CTFG agrees that ethical and local issues of CTAs are to be managed at the national level. We also remind that the single ECs opinion in each MS is mandatory and should be verified by the Commission. We think also that further guidelines on practicalities, harmonised dossier, time lines should be provided in order to better clarify and harmonise the ECs process and reduce work load for sponsors.

1.3.1. <u>Scope of the CAP</u>

The Commission reminds that a CTA covers 3 areas:
"*a. the risk benefit assessment as well as aspects related to quality of the medicines and their labelling.*
b. ethical aspects related to informed consent, recruitment and reward
c. local aspects related to suitability of sites, the investigator and national rules".
The Commission proposes that the coordinated assessment of a CT should only cover issues such as the benefit/risk assessment and aspects related to quality of the medicines and their labelling, including

- "*acceptability of the clinical trial in view of all anticipated benefits, compared to risks and inconveniences for trial subjects (including control group), 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, labelling, and importation of the medicinal products intended for the clinical trials;*
- *completeness and adequateness of the investigator's brochure*".

Issues relating to ethics (e.g. completeness and adequateness of informed consent, arrangement for recruiting subjects and compensation of subjects and investigators) and to local issues (e.g. suitability of investigators and of CT sites, insurance and indemnisation, compliance with rules on personal data protection) would be within the remit of MS.

It is up to the Member States to organise the remit and cooperation at a national level between the NCA and the EC's.

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

CTFG comments: CTFG is of the opinion that some items in the public consultation should be more precised (is the "design of the trial" covering the statistical assessment? Does the term "design" include suitability of the efficacy approach? Does the word "intervention" include the CT procedures?) or expanded (why limiting the risk assessment only to investigational medicinal products (IMP) and not to the other medicinal products to be used in the CT ? The investigator's brochure may be replaced by other documents in accordance with the CT1 guidance.).

The protocol should also be clearly listed in the coordinated assessment since inclusion/exclusion criteria, stopping rules, choice of dose, subjects monitoring and risk mitigation strategies in the protocol are to be clearly assessed in common.

Furthermore substantial amendments and safety data assessment (SUSARs, DSURs and other safety issues with potential impact on subjects' safety) of the initial application should be part of the CAP scope and further worked on.

Regarding ethics, the procedure to be followed for obtaining informed consent and the justification for the research with patients incapable of giving informed consent should be included in the revised legislation. The relevance of the trial and whether the evaluation (by the sponsor) of the anticipated benefits and risks is satisfactory is also an ethical issue.

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

CTFG comments: CTFG agrees with the idea to define exactly the scope of the coordinated/joint assessment.

Who is supposed to perform the coordinated assessment is an issue. The Commission proposes that it is done by the MS concerned by the CT (meaning either NCA or EC or both, up to the MS) and mixes up, in the scope proposed, items of interest for both NCAs and ECs such as the risk benefit and the relevance of the trial:

- pertinence of the CT from the perspective of adequacy of IMP and risk for subjects (quality, adequacy of posology and duration of treatment, follow-up procedures to minimise the risk),
- pertinence of the CT from the perspective of background scientific knowledge in the field, and from the perspective of involved risks derived from the CT taking into account normal clinical practice (type of follow up measures, adequacy of comparators),
- reliability of the CT design in order to make valid conclusions for which there are CHMP or ICH scientific guidances that the sponsor needs to take into consideration and the CT could be linked to a scientific advice.

Thus, the process needs to integrate the view from EC. This seems difficult with respect to the initial CT assessment, and turns out to be more complicated in case of substantial amendments.

CTFG believes this kind of confusion will not serve harmonisation.

We wish to restrict the assessment activity under the CAP to aspects in 1.3.1(a) that are assessed by all (or the majority) of NCAs; broadly similar to the current VHP.

Including aspects which may be assessed by Ethics Committees in a number of Member States within the CAP will create significant processing complications and complexities within the MS, including inconsistency with established arrangements for approval of other clinical research.
In particular, the relevance of the trial might be assessed as part of the ethical review under (b) rather than under the CAP, except wherever there is a national impact on matters within scope of NCAs such as subject safety and the regulatory context.

The legislation would rather define the scope of a common assessment by NCAs, whereas the rest of CT assessment being organised nationally. The NCA assessment should be focused on quality, efficacy and safety of medicines being used in the CT and safety of the subjects in the trial, taking into account:

- knowledge about quality, efficacy and safety of medicinal products (MP) intended for the CT, including IMPs and NIMPs:
- condition of use of MP, population of the trial, risk mitigation strategies and all interventions including procedures, in the protocol
- the protocol and the information available on medicinal products (IB or equivalent)
- the relevance of the trial including methodology, trial design and statistics
- substantial amendments and safety assessment (DSUR, SUSAR, urgent safety measures) are also part of the scope.

Another comment is about any 2nd round of MS that the sponsor might want to include in the trial. The process should propose a procedure that would make the initial coordinated assessment to be taken into account.

CTFG believes that there is a need to streamline the full process between NCAs and ECs to avoid confusion. Sometimes overlapping might be needed,, for instance regarding the ethical aspects of relevance of the CT.

1.3.2. Disagreement with the assessment report

In the CAP, the Commission proposes 3 ways to deal with disagreements among MS either by opting-out if justified by serious risk to public health or subjects safety, or MS concerned can vote with a decision based on the majority voting or by referring the matter to the Commission or EMA for a EU decision.

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

CTFG comments:
CTFG is in favour of the possibility for MS to opt out (as a last possible option) in case no consensus was established by the leaded RMS. The Member States that are positive with the clinical trial will approve it. The other Member State can in the first or subsequent rounds

negotiate with the RMS from the first round to request further information to meet their major concerns[1].

- The 2nd option would mean that a MS would be obliged to follow the majority and accept a CT to be conducted in its own territory despite its major concern.
- The 3rd one is not realistic because neither the Commission nor the Agency are responsible to assess CTs and if they were, they would be assisted by MS to do so. Any referral would lengthen the process and make the EU clinical trials unattractive than at present.

The CTFG proposal is:

- To achieve common decisions by a consensual approach, with emphasis on the RMS role to resolve all major objections

The Member States that are positive with the clinical trial will approve it. The others in the first or subsequent waves should negotiate with the RMS from the first wave to request further information or protocol changes to meet their major concerns. If the RMS fails to do so, those Member State will generally opt out in order to avoid different versions of protocol of the same CT.

1.3.3. Mandatory/optional use

The Commission considers 3 possibilities regarding the CAP:

- CAP is mandatory for all CTs;
- CAP is mandatory for all multinational CTs allowing mononational CTs to continue within the current CTD provisions;
- or CAP is optional, allowing sponsors to refer to national procedures.

Consultation item 7: which of these approaches is preferable?

The CTFG is of the opinion that CAP should be optional for sponsors at least for a transitional period .allowing them to use the CAP either for multinational CTs or for single country trials. Therefore the CTFG believes that starting a new mandatory process can have the danger of not being implemented.

1.3.4. Tacit approval and timelines

In this section the Commission covers several aspects:

- The tacit approval would not be possible under the CAP
- Explicit authorisation per MS would be mandatory
- Timelines for CTA should not be longer than today (as a general rules 60 days) and time lines for substantial amendments should be fixed.
- Timelines should be shortened for some CTs (so called type A trials) where the risk for subjects is minimal compared to normal clinical practice
- A definition of type A trials is proposed
- These types of trials would be identified in a pre-assessment.

Consultation item 8: do you think such a pre-assessment is workable in practice? Please comment.

[1] Also in rounds after the first round of CAP and in the case that RMS and MS do not come to an agreement as a last option either the opting out, meaning that the Clinical Trial will not be performed on their territory or there will be a solution negotiated between Sponsor and MS on the sponsors request should remain.

CTFG comment:

- The principle of explicit authorisation is acceptable, meaning that if no decision is taken within 60 days it is a refusal.
- Timelines in 60 days are acceptable for NCAs.
- Considering the national assessment (b + c) that would generally involve ECs, 60 days would not allow any clock stop and this may be not workable for ECs, due to their organisation based on meetings. Timelines of 60 days could be too short, depending on detailed CAP procedure, especially if work flow is sequential and not in parallel. For those reasons, the inclusion of a clock stop in the process might be discussed and limited to a certain period.
- Fixing timelines for SA is a step forward, as it is currently laid down in most of national legislations and in the VHP (35 days).
- Shortening time lines for "low risk" clinical trials (type A) is also supported but those timelines should be clarified.
- The idea of pre-assessing the classification as type A CTs is acceptable but might need further clarification such as: who is responsible, when is it done (before the CTA? During the assessment period? in which timelines?), how to ensure harmonisation of such classification.

CTFG supports the risk based approach for simplifying processes and proposes that:

- The sponsor justifies in the CTA its proposed classification by the means of criteria and process developed by the CTFG
- This classification is reviewed and validated/coordinated on a case by case basis by the CTFG in order to ensure harmonisation in EU and also in the further assessment of the CT. We do not support the idea that the classification is assessed by committees which are not involved in the approvement process of CTs.
- Time lines for classification are clarified in order that the time gained by the shorter assessment for type A CTs is counterbalanced by the time needed for the pre-assessment.
- A pilot phase could be set up as soon as possible and the CTFG can offer to do it in the VHP.

The Commission should clarify the process to classify the study and particularly the role of the PRAC with respect to the borderline non interventional CT.

Regarding the definition of type A CTs, CTFG would like also to raise several points:

- This definition should be reviewed in order be the simplest and also to be in line with other current reflexions (OECD,…).
- It should be said that the IMP is not modified for the CT
- "indication" should be replaced by "conditions" (including indication but also dose, safety monitoring measures).

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

2.1. Limiting the scope of the Clinical Trials Directive

2.1.1. Enlarging the definition of "non interventional" trials

Commission 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.

CTFG comments : CTFG agrees not to modify the definition of non interventional "trials which is rather clear but to proportionate requirements for clinical trials, on a risk-based approach (such as simplified processes for type A trials).
However, we should not talk about non interventional trials but about non interventional studies.
Furthermore, detailed guidance should be given to harmonise the interpretation by all the stakeholders of "additional diagnostic or monitoring procedures" taking examples of the most frequent additional procedures (questionnaires, mere blood samples, certain diagnostic measures…). An agreed list of interventions of minimal risk might help to harmonise potential differences between MS.

CTFG recognises the importance of non interventional studies in improving knowledge on medicines. This is why we would be also in favour of standardising general principles for good practices of non interventional studies.

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

Consultation item no. 10: Do you agree with this appraisal? Please comment.

CTFG comments: CTFG strongly supports the principles to proportionate requirements for clinical trials rather than excluding academic trials from the CTD.

In the case of non-commercial or academic sponsors the aim of the CT might be the optimising a therapy with products holding marketing authorisations, but it might also be a First in Human application of cell based product or a gene therapy. Therefore also risk minimisation according to the sponsor status is considered impossible.

Two standards of protection for the participants of clinical trials and for the data (GCP standards) would not be acceptable. In the case of non-commercial or academic sponsors the aim of the CT might be the optimising a therapy with products holding marketing authorisations, but it might also be a First in Human application of cell based product or a gene therapy. A differentiation between commercial/ non-commercial sponsors is inappropriate to ensure the protection of the participants and to ensure data reliability.

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

Commission 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.

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

The Commission proposes risk-adapted rules not only for time-lines (see 1.3.4), but also for the content of the CTA dossier and safety reporting. Those rules could be included in legal text of the Directive or in the annexes (as implementing measures). To draw up the risk-based approach, the Commission proposes to consider:

- the risk to trial subject safety compared to normal clinical practice;
- the risk to data reliability and robustness;
- the international harmonisation work such as the ICH guidelines and also the last drafts of CT1, CT2 and CT3 guidance.

CTFG comments:

CTFG still supports the proportionality of requirements based on the risk of the CTs. CTFG also supports the 2 pilars defining the risk (risk to CT subjects, risk to data reliability). We also think that:

- other processes could be adapted to the risk (e.g. labelling/IMP traceability systems for some phase IV CTs ; monitoring, insurance),
- rules to adapt safety reporting are not provided in the draft CT3 currently under review (as far as we know). Therefore CT3 should have to be revised.
- are ICH guidance to be applicable for academic trials?
- other guidance, from EMA for instance, should be referred to.

The CTFG support the proposal to remove from the main text of the Directive and annex certain elements that are likely to be subject to adaptation, such as the content of trial application dossiers. Under Treaty of Lisbon these would need to be amended/updated by means of delegated acts. We would like to ensure, however, that Member State experts would always be consulted and their views taken into account when delegated act provisions in this area are proposed by the Commission. Otherwise we believe that relevant points have to be addressed in the directive.

To sum up, CTFG recommends that major aspects of CTs are regulated within the Directive and only minor administrative aspects are clarified by the guidance and in accordance with the MS.

CTFG proposes other issues to be covered by the CTD revision:

- The legislation should set up also a safety assessment coordination by the MS (SUSARs, DSUR and other safety issues) , submission (eg DSUR single repository…) and should take into account the MS needs in terms of IT (eg CTFG needs on Eudravigilance CT module/EVCTM expressed to the Commission and EMA in 2010)

- The Commission should consider whether to exclude an explicit reference to the Declaration of Helsinki in the version 1996 which is confusing. Whilst it is essential that the rules for approval and conduct of clinical trials respect the principles that underpin the Declaration, and the legislation should make that clear, we propose that reference to any particular version of the document should not be necessary and could cause continued confusion.
- Rules and processes regarding safety reporting should be further reviewed (e.g. DSUR single repository; DIBD notification; simplified SUSARs reporting to ECs)
- Requirements and standards on safety and quality of trial should be independent of risk and should be state of the art accordingly
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- Annex 13 should include derogations on labelling for certain trials with the possibility to use other traceability tools.

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

Commission Preliminary appraisal: This combined approach (new definition for the 'investigational medicinal product' and establishing rules for 'auxiliary medicinal products') 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.

CTFG comments:
Clarification of the IMP definition is welcomed. However, the placebo should be maintained as an IMP in the new definition proposed by the Commission.

The definition of auxiliary medicinal products could be "A medicinal product as referred to in Article 3(3) of Directive 2001/83/EC, which is not an investigational medicinal product and which is fixed by the clinical trial protocol".
Clarification should be given on non-approved challenge agents and also on non-CE marked medical devices which are to be used in a CT.

2.4. Insurance/indemnisation

Commission Preliminary appraisal: Both following 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?

No CTFG comment

2.5. Single sponsor

Commission Preliminary appraisal: In view of the above, option 1 (maintaining the concept of a single sponsor) 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.

CTFG comments:
The CTFG supports the single sponsor concept in EU but also the delegation of tasks defined in question and answer 2.3 of the Commission (volume 10)
We propose that the revised Directive make a clear distinction between "responsibility" for the conduct of a trial and "liability" in the case of damage to a trial participant. Responsibilities for study oversight would need clearly to be defined. The CTFG agrees that improved harmonisation of procedures will go some way to resolving current difficulties

2.6. Emergency clinical trials

Commission 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.

CTFG comments:
CTFG welcomes the suggestion to allow and harmonise the conduct of CTs in emergency situations.
Regarding the modalities proposed, the CTFG invites the Commission to integrate the conditions laid down by article 5 of the CTD and to take into account the principles of the declaration of Helsinki (article 27), of the convention of Oviedo and of the additional protocol to the convention on human rights and biomedicine, concerning biomedical research, in particularly:
- the impossibility of carrying out instead research of comparable effectiveness on individuals capable of giving consent,
- these individuals must not be included in research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject (same disease or disorder or condition),
- the research entails only minimal risk and minimal burden.

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

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

- ***Codifying, in the revised legislative framework, the provision in point 2.7.2.4.of the detailed guidance CT-1 (statement of GCP compliance and reference to the entry of this clinical trial in a public register) ;***
- ***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.(20).***

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

CTFG comments:

CTFG reminds that CTs submitted in a CTA are to be conducted in accordance with ICH- GCP requirements.

CTFG agrees that CTs performed in 3rd countries and being presented in a CTA dossier in EU should be publicly available. However, the CTFG would accept a publication not only in the EU CT registry (EU-CTR) but also in any other public registry.

4. Figures and data

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.

CTFG comments:
CTFG thinks that figures on CTs in EU should be extracted from the 2 European databases which represent today the only tools to allow an overview of the current situation of CTs in EU.

EudraCT would also allow MS to get data on the number and nature of IMPs being tested in EU which would be usefull for assessment organisation matters (eg by indicating the number of DSURs in EU or the number of new IMPs per year or the number of IMPs with MA giving the number of type A trials….)
EVCTM is also able to give the current figures on SUSARs.and other interesting information on safety issues. Those figures should be publicly available