EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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European Medicines Agency supplementary response to the European Commission's Concept Paper of 9 Feb 2011 on the Revision of the 'Clinical Trials Directive' 2001/20/EC

Introduction

The European Medicines Agency (the Agency) welcomes the initiative of the European Commission in continuing their preparation for the revision of the clinical trial legislation by way of discussion documents on the key issues.

A coherent, effective, efficient, benefit and risk proportionate regulatory process that can assist the development of products from their inception, through scientific advice, first in human trials, and full clinical development is an important element in enhancing the European research environment and public health network.

The new legislation should be clear in its definitions and requirements, avoiding the need for extensive clarification in guidelines.

Consultation Topics

1. Cooperation in assessing and following up applications for clinical trials (response to items 1-8 of the Commission Paper)

A **single EU portal** for clinical trial application and oversight should be considered a pre-requisite for an improved application process, regardless the architecture of the clinical trial authorization procedure.

The best review procedure should not be a confrontation of centralized versus non-centralised processes, but should establish the best use of expertise in the EU regulatory network, strike the most efficient balance of administrative (including IT) support, and set a rational balance between issues that could be addressed at EU level in a collective manner and those that are best addressed at national level.

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The Agency supports a strong, coordinated assessment of multistate trials involving the concerned member states. This offers the more effective solution taking into account that 17% involve 2-6 MSs and 5.4% involve 7-12 MSs whilst 76% of clinical trials involve only one member state (MS).

The process should support both the regulatory/scientific assessment by the competent authority and the ethical/medical assessment by the ethics committees. Whilst truly ethical issues are a national prerogative, much could be done to simplify and harmonize the administrative processes involved and to assist ethics committees in coordinating their evaluations, since in reality there are few issues on which real ethical divergence exists between member states. A coordinated, independent ethical assessment by representatives of the ethics committees of the concerned member states should be envisaged for multi-state trials.

The number of clinical trial applications involving 1, 2, 3 etc member states is shown in the table below (data from EudraCT):

Number of Member States involved per Clinical Trial FPP 2004 to 2009

Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	Total
2004	535	110	83	62	51	51	32	19	14	12	7	3	5	4	1			2							**991**
2005	2,974	280	194	115	95	74	72	48	32	23	23	16	6	8	7	2	5	1							**3,975**
2006	3,297	274	165	118	107	85	71	52	35	28	22	15	25	7	10	8	6	5	2	1	2		1		**4,336**
2007	3,858	293	181	149	97	86	78	61	51	42	30	31	18	20	10	7	3	6	1	3	2		1		**5,028**
2008	3,538	265	159	135	103	97	61	59	44	36	24	30	15	13	13	5	4	3	5	1	1	2	4	1	**4,618**
2009	3,549	244	174	109	98	74	58	48	41	19	24	15	12	9	6	1	4	2	1	1			1		**4,490**
Grand Total	**17,751**	**1,466**	**956**	**688**	**551**	**467**	**372**	**287**	**217**	**160**	**130**	**110**	**81**	**61**	**47**	**23**	**22**	**19**	**9**	**6**	**5**	**2**	**7**	**1**	**23,438**

The future EU clinical trials system can then be composed of:

- Single EU portal for clinical trial applications, used for all clinical trials (including single state trials) and supporting competent authority and ethics committees processes.
- A single decision per clinical trial, issued by each member state, based on the combined but independent EU and national review outcomes of the competent authority and ethics committee evaluations. All EU and local assessments should be completed and lead to a decision in all concerned member states within the 60 day timeframe.
- National approval of single state trials.
- Coordinated assessment of multistate clinical trial applications by the concerned member states:
  - Coordinated quality, safety and efficacy assessment by the competent authority experts of the member states concerned by that application.
  - Coordinated, independent ethical assessment by representatives of the ethics committees of the concerned member states.
  - The outcome of both coordinated assessments at EU level should be legally binding on the concerned member states, for the scope of issues assessed in the coordinated process. If a member state should not agree it would have to opt out (see below).
  - For each assessment procedure a lead member state would be selected. Where a series of protocols are envisaged in a clinical development programme the applications could be linked so that the combined group of concerned member states could be progressively involved. The process should make use of the best available expertise and facilitate the use of experts from other member states, not concerned by that trial application, where appropriate.

  - Local evaluation in each member state with respect to the investigator sites and facilities, translation of information for trial subjects, additional local information to be provided (e.g. related to data protection), and issues relevant to national medical practice. Additional investigator sites could be added later as simple local amendments.
  - The overall process should ensure that the same protocol is authorized in all member states where the trial is to take place and the same core information to trial subjects.
  - For trials of risk type A involving products with marketing authorization in the member states concerned, the system could involve application to the single EU portal, and a review only by the ethics committee procedure (EU and local). The risk assessment would be made by the sponsor and validated by the ethics committee process, based on agreed criteria. The single decision would again be delivered by each concerned member state within 60 days.
  - The application process would ensure that all clinical trials would be registered and made public with up to date information in the EU CTR, providing a summary data set, in line with applicable guidance in relation to provision of public information on clinical trials in the community.
- Secretariat at the Agency to support the assessments, the functioning of the network, operate the IT system, support the administrative process, operate a help desk for sponsors/researchers preparing or processing applications etc.
- A single working group for clinical trials to replace the current CTFG, Commission ad hoc working group, EudraCT TIG and EV CTM TIG/WG.
- A new working group of ethics committee representatives to develop and harmonize the activities of the ethics committees in the context of clinical trials, in a similar way to the WG on clinical trials.
- These two working groups would work jointly to ensure that administrative and IT processes and the respective roles of each, and communication between them, are effectively set out and well integrated.

Disagreement with the assessment report

Disagreement with the coordinated assessment should be resolved by consensus where possible but if that is not achieved a member state may opt out.

A trial may also be refused in one member state and not in others if the outcome of the national aspects of the evaluation was negative.

Opt-out gives member states the assurance that in the small number of cases where they consider a trial would not be suited to their local situation that they could opt-out. If one Member State opted out initially, the sponsor could re-apply to them as an additional member state, thus allowing the possibility for the outstanding issues to be resolved. Any change to the protocol would require the agreement of all member states involved through an amendment.

Activities post-authorization of a clinical trial

Following an initial procedure involving one or more member states the appointed lead member state would continue as lead. Additional member states could be included in a trial through evaluation of the original assessment and agreement with that. Any objections requiring a change to the protocol would require the agreement of all member states involved through an amendment.

Substantial amendments to the protocol or other common elements of the procedure should follow a similar process to the initial one but with a shorter timeframe. The timeframe for assessment of substantial amendments should be reduced (e.g. 30 day maximum).

For drug safety assessment a single lead member state would be appointed per active substance. SUSARs and related safety information on that active substance/products should be evaluated by the same team of experts. The assessment would be shared with each member state concerned by trials of that substance for comment and questions. The competent authorities would inform the ethics committees of the outcome of the assessment and warn the EC in cases where significant new safety issues are arising.

In a similar way the same IMPD may be relevant for several trials and any changes to the IMPD should be evaluated by all member states concerned by those trials, and led by the same lead member state.

Changes to investigator sites, local study arrangements, indemnity or insurance and local aspects of information to subjects should be addressed by each member state at national level, respecting common EU timelines and requiring assessment by the relevant bodies (CA and EC, EC only amendments or CA only amendments).

Funding of the procedure

- A fixed percentage, to be established, of the annual fee for marketed products should be allocated to subsidizing the clinical trial system – this is reasonable as it balances the cost of research by the benefit of those research projects that are ultimately successful. It should cover development of the single portal, operation of the working groups and of the secretariat.
- A scale of fees should be established to ensure proper funding and operation of the individual assessment procedures.
- For single state trials the level of fee should be established by the member state concerned.
- For multistate trials a sliding scale of fee should be applied so that each additional member state involved incurs a smaller additional amount.
- A reduced fee or no fee could be applied in the case of clinical trials run by state bodies, non-profit organizations or companies with SME status.

Single EU Portal for clinical trial applications

The single portal for clinical trial applications would include all documents and translations required for both competent authority and ethics committee review of the clinical trial. 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. Irrespective of the subsequent authorization process such a single EU portal would be an important step forward in the clinical trial application process. The existing IT systems operated by the Agency, including EudraCT, EV CTM, EU CTR, EudraNet, MMD, EURS and the list of information on authorized medicinal products now being put in place as part of the implementation of the pharmacoviglance legislation, can contribute to the establishment of an effective platform for such a portal, which should be established by the agency using the relevant functionality of the existing systems.

- User accounts for sponsors/applicants to enable applications to be compiled, submitted and maintained (information updates, (substantial) amendments, DSURs addition of new sites, addition of new countries etc..).

- A secure work area for each sponsor / agent to prepare applications and load documents or information as they become available and prior to submission, to both ethics and competent authority processes.
- An eCTD like structure to hold the various forms, documents, translations etc. to include all required documents.
- In order to avoid multiple parallel systems, redundant investment in systems and processes, and confusion among sponsors, the singe EU portal should be used for all trials, where mono- or multistate.
- Produce publically available information on clinical trials summaries of results via EU CTR.

Mandatory/optional use of the portal and of the coordinated assessment procedure

Optional use would risk leading to a divergence of processes and activities and to multiple parallel administrative and IT processes being established.

The present system is maintained and progressively enhanced by the following steps:

- The core functionality of the single EU portal, which should include submissions for competent authorities and ethics committees is established and mandatory for all trials.
- Coordinated procedure for competent authority assessment is established as optional for all multistate trials. The coordinated ethics procedure should be added after two years of operation of the single portal and coordinated competent authority assessment.

These steps should be introduced at fixed intervals, but altogether within 3 years of entering into force of the new legislation. The scope should be reviewed after 5 years (e.g. as an annex to the legislation).

Tacit approval and timelines

The timeline for the overall procedure from application to decision by all concerned member states (including both competent authority and ethics committee aspects) should be sixty days and without clock stop or added time. Member states should be able to provide shorter time frames for single state trials, at their discretion.

For Type B trials (phase I-III) the process should require the explicit approval of both competent authority and ethics committee.

For Type A trials (phase IV, and a range of treatment optimization and similar trials of marketed products), the system relies on the established quality and safety of the marketed product and a risk assessment. Such trials should only require ethics committee review (in the case of multistate trials using the EU and national elements of the procedure). They would still use the single EU portal and thus ensure application to the ethics committee process, notification of the trial to the system and public register, and notification to the competent authorities via the EU portal. The trials could proceed once the ethics committee positive opinion is delivered, and in this case that would form the national decision for each member state concerned by the trial. In exceptional cases the competent authorities could place a study on clinical hold if significant concerns regarding safety or efficacy arose.

The possibility of an expedited clinical trial approval process should be foreseen for urgent public health reasons.

Scope of assessment

The following grouping of issues to be reviewed is suggested:

- Coordinated Assessment – competent authorities:

  The risk-benefit assessment, as well as aspects related to quality of the medicines and their labeling including:

  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 relevance of the trial, including the credibility of the results and their relevance to special populations (based in particular on age);

  - compliance with the requirements for manufacturing and importation of the medicinal products intended for the clinical trial;

  - compliance with the requirements for labeling of the medicinal products intended for the clinical trial;

  - completeness and adequateness of the investigator's brochure.

- Coordinated Assessment – ethics committees:

  – trial design and relevance, medical practice;

  – completeness and adequacy of the information submitted to obtain informed consent.

  - consideration of age discrimination.

- Local EC review of suitability of sites, the investigator, and national rules. This includes the following:

  - specific ethical principles with local relevance (e.g. relating to use of stem cells);

  - local medical practice;

  - suitability of the investigator and of the clinical trials site;

  - adequacy and completeness of the insurance or indemnisation covering the investigator and sponsor;

  - local information/informed consent issues - suitability of the translation of informed consent and the consent process, compliance with the applicable rules on personal data protection;

  - arrangements for rewarding and compensation of investigators;

  - arrangements for the recruitment of trial subjects including any payments and facilitation measures for mobility- or cognitively-impaired subjects.

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

Enlarging the definition of 'non-interventional trials'

- The current system sets out a dichotomy in which a study is either an interventional or a non-interventional clinical trial. There is a range of studies which should not be considered clinical trials within the meaning of the Directive 2001/20/EC. This includes studies involving retrospective data analysis, cohort observation or use of registries. This category should be clearly defined, avoiding the need to designate them as interventional or non-interventional.
- Where a study is considered to be a clinical trial the concept of intervention should be restricted to that of intervention in the pharmacological sphere/treatment decision – i.e. where a subjects treatment with one or more medicinal products is determined by the trial protocol. Where that is not the case, the presence of other interventions such as additional blood samples, visits, questionnaires etc should not convert a non-interventional trial into an interventional trial of a medicinal product.
- The implementation of the new pharmacovigilance legislation and in particular Good Vigilance Practice and the implementation measure on post-authorisation safety studies should be used to establish better, and harmonized standards for the conduct of these non-interventional trials, including situations where there is a need for them to be submitted to ethics committees, for example in cases where additional non-pharmacological interventions are foreseen.

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

The same requirements should apply to all sponsors. A risk adaptation of the requirements for clinical trial application and supervision is now the consensus approach to addressing the issues that have been raised in the past.

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

Risk adaptation should address the protection of trial subjects and the quality and robustness of the trial data.

The level of oversight required should be based on Type A and Type B trials, where Type A are trials with marketed products in Phase IV, or within established therapeutic guidelines or treatment optimization studies. Such trials should only require ethics committee approval and notification to the competent authorities via the single portal, which includes public registration. The competent authority would have the possibility, in exceptional circumstances, of placing a trial on clinical hold should safety or efficacy issues require that. The ethics committee should be able to withdraw its approval.

The approach should ensure that the risk benefit analysis of the trial takes into account the risk of the trial subjects underlying condition and not only the absolute risks of the interventions foreseen by the trial.

The quality and robustness of the data should be addressed by better risk adaptation of the application of good clinical practices. These approaches can be adapted to the phase of the trial and to the risks inherent in the trial to the subjects and data.

Clarifying the definition of 'investigational medicinal product' and establishing rules for 'auxiliary medicinal products'

There are four types of product to be differentiated:

1. **IMPs**. The definition of IMP might be narrowed to *'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, **including placebo**.'* However the effect of removal of the text *"including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorised indication, or when used to gain further information about the authorized form;"* should be tested in different scenarios to avoid unintended consequences. The relation between the IMP definition and that of background treatment (see 3 below) should be carefully considered.
2. **Medicinal products which are used at the request of the protocol but are not IMPS** – in particular escape medicines and some medicinal products that might be used as challenge agents or as diagnostics. To the extent they have a marketing authorization, which is usually the case, the controls are the recording of their use, and they should be subject to the clinical trial safety reporting, as for IMPs, since they are used explicitly for the purpose of the trial.
3. **Medicinal products which are background therapy** – in other words they are the treatment that the trial subjects would in any case have been provided with. These should not be considered as falling under article 3(3) of Directive 2001/83/EC, which is more specifically intended to mean IMPs, since they are not *"intended for research and development trials"* but are in use in any case. They are by far the most common of the products currently referred to as NIMPs, and are the ones requiring the least additional control since they would in any case have been prescribed. The only control being to record their use as concomitant medication, in the medical record and CRF. It may be a condition of the protocol that subjects to be recruited should be assigned to a particular standard treatment or regime, which would be part of the background treatment. Adverse events relating to such products would be recorded and reported to the sponsor by the investigator and included in the clinical study report in accordance with current requirements. Normal pharmacovigilance reporting should apply to such products.
4. **Products without a marketing authorization** which are used as challenge agents. For these products additional information on quality and safety should be provided, and the pharmacovigilance reporting should be the same as for IMPs, since these products are not covered by another regime.

Insurance/indemnisation

The proposed option of indemnisation of trials by the state would offer a good solution. The current status creates a complex array of requirements, and more critically leaves institutional bodies or individual researchers very reluctant to undertake or sponsor research, because of a fear of liabilities where in practice the risks of liability prove to be very limited. This concern would be alleviated by such a proposal.

Single sponsor

It is suggested that a better separation of sponsors' responsibilities, from the various liabilities (product or professional) that arise would be helpful, as will a solution regarding insurance/indemnity.

A legal possibility for different legal entities to act as sponsor at a national level, but combine their activities in a shared manner in international trials would be one possible approach. Networks of researchers should have the possibility of combing to form an entity that takes on the sponsor role.

Emergency clinical trials

Research in emergency situations is clearly an area that requires support and good regulation. The area is one in which life saving or disability preventing therapies are the main focus and for which clear evidence is needed for new therapies.

The proposals of the Commission will greatly benefit this area of research. In finalizing the legislation proposal the Commission should take into account that the more urgent the therapy required, the more likely it will be that it needs to be given at the place where the patient has suffered trauma – i.e. at home, in the workplace or in the street, by the emergency services. The legal provisions should not preclude this possibility – which in some cases may be administered by paramedical staff, without the physical presence of a physician.

One element of compensating for the inability to obtain consent would be to have full transparency on the conduct of the trial in advance in order to inform the public in the Member States where the trial is to be conducted.

The inability of the trial subject to consent should be the consequence of their trauma and not of their underlying status a minor or subject already mentally impaired. The urgency to proceed with treatment should preclude a delay in which the consent of a legal guardian, or the person themselves would be possible. The trial should not be possible in another population where consent could be obtained. The trial should take place where there is equipoise in relation to the treatment arms and objective of the trial and there is potential benefit to the participant or the group to which they belong.

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

The Commission proposal to require prospective registration of clinical trials in a public register before their results can be accepted in support of a MAA or CTA application in the EU is welcome. The EU CTR should be opened to permit registration there but other registers should also be accepted – it is suggested that the Commission proposal consider those registers accepted as primary registers by the WHO ICTRP should be acceptable.

The Commission should consider widening the scope of EudraCT and EU CTR so that other clinical trials could be included, on a more voluntary basis, as a support to European clinical research.

4. Figures and data

EMA will provide some data from EudraCT in a separate document.