

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

ECRIN (European Clinical Research Infrastructures Network)
EORTC (European Organization for Research and Treatment of Cancer)
ESF-EMRC (European Science Foundation - European Medical Research Councils)
CPI (Coordination des Promoteurs Institutionnels)
INSERM (Institut National de la Santé et de la Recherche Médicale)
VISEAR (Vienna Initiative to Save European Academic Research)
ESICM (European Society of Intensive Care Medicine)

Aspects of the Directive 2001/20/EC that work well

- 1) The EU legislation resulted in a **partial harmonisation** of clinical trials on medicinal products in the EU. There is now a need to extend the harmonisation process to all the categories of clinical research in the EU, beyond clinical trials on medicinal products.
- 2) The EU legislation also led to the **integration** of clinical trial identification (through the unique EudraCT number and database) and of adverse event reporting in clinical trials (through the EudraVigilance database). Such databases should now be used to promote transparency, and particularly to develop a European tool for open study registration and reporting.
- 3) The EU legislation promoted a **single opinion** from ethics committees at the national level, and defined the roles and responsibilities of the sponsor and of the state (through the competent authority) in the conduct of clinical trials. There is now a need for a better definition of the respective roles of ethics committees and of competent authorities, and for streamlining their interaction.
- 4) As a consequence of the Directive, some EU countries have invested in the development of a clinical research **infrastructure** and promoted **training** programmes, whereas some public institutions have strengthened their capacity to fulfil the **sponsor's tasks**. This resulted in an improvement in the conduct, in the quality and in GCP compliance of clinical trials. The development of such clinical research infrastructures (at clinical sites, at clinical research centres, at clinical trials units undertaking design, conduct and analysis of clinical research) should now be supported in all the EU member states and coordinated at the EU level.

Aspects of the Directive 2001/20/EC that do not work well

1) **Harmonisation / integration**

The 2001/20/EC Directive and its transposition into national legislation failed to efficiently harmonise the regulatory framework and to facilitate EU clinical trials. It made the initiation and conduct of national, and also of multinational clinical trials on medicinal products more difficult than before the implementation of the Directive. The increased administrative

workload and expensive monitoring raised the cost of academic clinical research by 2 to 4 times, and made it impossible to conduct some studies. Moreover, acting as a single sponsor in the EU is impossible for most academic institutions.

Considering the failure of the 2001/20/EC Directive to efficiently harmonise the regulatory framework of clinical trials, and the failure of national legislations and national competent authorities to implement harmonised regulation and practice, we would recommend, whenever possible, an integrated approach (ie, for the competent authority). When integration is not possible (ie, for ethics committees), coordination, guidance, and accreditation should assist and enforce harmonisation. In addition, implementation of such legislation should be coupled to a strengthening of the clinical research infrastructure and of training programmes at both the national and the EU levels.

2) Directive / regulation

Some EU member states took advantage of the flexibility in the transposition of the Directive to escape part of its negative impact on clinical research. This resulted in divergent national regulations that made multinational cooperation even more difficult.

In an ideal situation where the new EU legislation would foster rather than hamper clinical research, the issue of a real harmonisation should be addressed by the new legislative framework, either through a Directive, a regulation, with clear implementation guidance. Most participants consider that the regulatory framework for clinical research can be covered by a regulation, avoiding divergent interpretation while transposed into national legislation – in such case, a Directive should be maintained for ethics committees, as ethics is left to the competence of the member states and cannot be covered by an EU regulation.

3) Field of the Directive

Clinical research is not restricted to clinical trials on medicinal products – this is particularly true for academic research. There is a major disharmony between national regulations regarding clinical research other than clinical trials on medicinal products. This leads to consider the need for extension of the EU legislation to areas of clinical research not covered by the Directive. However some countries fear that such an extension would hamper rather than facilitate such research.

The ideal solution would be a single EU legislation designed to facilitate clinical research in the EU, prepared by DG SANCO, DG Research and DG Enterprise and Industry, adequately and equally protecting the participants in every category of clinical research across the EU (a situation equivalent to the national one where the Ministry of Health is usually responsible of such legislation). If such a solution is not possible, we would suggest:

- to extend the field of an improved version (assuming that it really facilitates clinical research) of the EU legislation on medicinal products to all the clinical trials on health products (including medical devices, diagnostic products, herbal medicines, nutritional supplements), as they require a common regulatory framework in which the competent authority supervises the health product and the preclinical requirements, and the ethics committees supervise the protection of participants.

- to write a new legislation (also assuming that it really facilitates clinical research) covering all clinical research not involving health products (also reviewing the preclinical development of know-how and procedures), either interventional or observational, in order to ensure harmonised adequate protection of participants and to facilitate clinical research in the EU.

This new legislation should involve DG Research and DG SANCO.

4) *Competent authorities*

The task of the competent authorities is to supervise the medicinal product, which is the same throughout the EU. There is still a considerable disharmony between requirements for clinical trial authorisation from the competent authorities. The practices differ between countries. There is a redundant assessment of the same product by many agencies, resulting in waste of time, money, and expertise for the agencies, and in multiple submissions for the applicant, and most importantly in a delay for a new therapy to benefit patients.

For multinational trials, the easiest way to circumvent this difficulty would be to obtain a single clinical trial authorisation through a centralised procedure (or a mutual recognition) in which the clinical trial application is managed by one single competent authority, instead of up to 27 national competent authorities. This would save a lot of time and human resources, avoid duplication of protocol and investigational medicinal product (IMP) dossier review, strengthen expertise, and reduce the administrative burden for academic sponsors and investigators. This is merely an extension of what is proposed for first-in-man studies.

For national trials, the clinical trial authorisation could be left to the national competent authority, however, in the long term integration of clinical trial authorisation will make sense (as EudraCT and SUSAR reporting are already integrated) also for national trials.

The governance of EMEA (and/or a new EU competent authority) should be modified towards more consideration of the interests of consumers, public health issues, and research issues – in the member states, the medicines agencies depend on Ministries of Health, not on the Ministries of Industry.

5) *Ethics committees*

Ethics committees ensure the protection of participants in clinical trials. There is a major disharmony in the assessment of clinical protocols and informed consent forms by ethics committees. This reflects cultural differences in ethical review of clinical research but additional, unnecessary disharmony is due to the lack of coordination, training, and quality assurance systems.

The EU legislation should promote harmonisation of the activity of ethics committees through either a guidance or a change to the Directive implementing an appeal procedure and an accreditation system for ethics committees, ensuring appropriate training and quality assurance, based on EU-wide specification. In addition, a European coordination of ethics committees (under the responsibility of DG SANCO) should promote harmonised training, tools, and practice, including a common template for the informed consent requirements in the EU.

6) *Multiple sponsors*

A single clinical trial authorisation, and a single EudraCT number, should not necessarily require a single sponsor in the EU, only a single applicant at the EMEA/EudraCT level. The requirement for a single sponsor is a major bottleneck to multinational clinical research for academic institutions that lack the capacity to fulfil sponsor's tasks in multinational studies. This is also true for small and medium-sized enterprises (SMEs). In addition, some countries allow multiple sponsors.

There is an absolute need to allow multiple sponsorship, for multinational as well as for national trials, in order to share, on a contractual basis, the roles and responsibilities in the various EU member states, this multiple sponsorship being under the coordination of a single applicant for European regulatory authority.

7) Definition of categories of research

Some definitions are open to divergent interpretation, resulting in national differences in the categorization of the same clinical study, particularly the border between interventional and observational studies.

The Directive defines intervention as treatment intervention, diagnostic intervention, or change in follow-up ('monitoring') procedures. This led to divergent interpretations between countries, as some consider diagnostic procedures as intervention in any case, other only if they increase the risk for the patient, whereas other have defined an intermediate category of 'minimally interventional' studies. As a result, the same post-marketing safety study, without treatment intervention but with collection of a blood sample, may be regarded as a clinical trial on a medicinal product covered by the Directive in some countries, and as an observational study in other.

The Directive fails to differentiate categories of research on medicinal products, and does not consider the lower risk associated with some of them, (particularly post-marketing studies, which represent a major part of academic clinical research). Instead, it proposes adaptation for 'non-commercial trials'.

There is a need to clarify the border between interventional and observational studies. Therefore, a workshop should be organised to discuss this point and the potential relevance of defining a category of 'minimally interventional' studies, without treatment intervention and with only low-risk intervention regarding diagnostic or follow-up procedures, for which approval from ethics committee is required, without full clinical trial application.

There is also a need to harmonise the interpretation on psychological assessment as an intervention.

In a more general perspective, there is a need to refine the definition of categories of clinical research, beyond the phase I-IV classification. The regulatory requirements should take into account the lower risk associated with studies using marketed drugs within their labelled indication for treatment optimisation or combination trials, or trials on off-label use of marketed drugs. This is of utmost importance for the academic community as a considerable part of its clinical trial activity falls into these categories. Developing regulatory requirements based on the risk associated to these categories would be an alternative way to the 'specific modalities for non-commercial trials' that tend to suggest that there are two levels of quality. We strongly oppose the idea that clinical trials should come in different forms regarding their quality, depending on who initiated the trials. If clinical trials are to differ in any regard, this ought to be decided based exclusively on a thorough risk assessment (hazards to the participants, to the trial's data, to public health). A workshop should be organised to help further discuss this critical point.

There is a need to clarify the border between medicinal products, nutritional supplements, and nutrition studies. A workshop should be organised to help further discuss this critical point.

The Directive uses the wording 'subjects' for individuals participating in a clinical trial. This should be changed to 'participants', which better highlights their active role and is non-derogatory.

8) Definition of 'non-commercial' trials

The concept of commercial compared to non-commercial trial should be replaced by a better wording (avoiding 'commercial').

In addition, the need for support and for regulatory adaptation may be different for 'non-commercial trials' and for 'trials sponsored by a non-commercial institution'.

There is a need to organise a workshop on the definition of clinical research run by academic institutions (e.g., investigator driven clinical trials), and to determine, with representatives of the academic research community, which adaptation could be proposed, for which type of trial.

Defining 'specific modalities for non-commercial trials' tends to suggest that there are two levels of quality. This should be avoided, and in turn risk-based strategies should be used to improve the cost-effectiveness of clinical trials, especially for monitoring. Therefore developing regulatory requirements adapted to the risk associated to defined categories of clinical trials would be an alternative way.

As stated in (7), most clinical trials sponsored by academic institutions correspond to categories of research associated with a lower risk: studies using marketed drugs within their labelled indication for treatment optimisation or combination trials, trials on off-label use of marketed drugs, pharmacoepidemiology studies. Academic institutions are also involved in the development of drug treatments for rare diseases, where market incentives fail to drive industry investment. Public-private partnership is frequently used for co-funding or co-development. Specific modalities should be defined for all these categories of research, not for 'non-commercial trials' as a whole.

9) Adaptations for academic research ('non-commercial trials')

Academic institutions acting as sponsors in clinical research face major difficulties in either national or multinational trials, that may be dampened by measures ensuring an appropriate level of quality, and based on support and on regulatory adaptation depending on the risk associated with the category of study (hazard to the patient, hazard to the institution, hazard to the study, hazard to public health).

The guidance document on 'specific modalities for non-commercial trials' mentioned in recital 11 of the 2005/28/EC Directive states that data from non-commercial trials cannot be used for registration, which is a major obstacle to academic-sponsored research and to the development of new indications for marketed medicines, especially in rare diseases. In the future, this may be a threat to all diseases due to the development of personalised treatments.

In some countries, non-commercial trials (or sponsors) are waived to pay fees to competent authorities and to ethics committees. Other countries do not implement such a waiver, or only reduced fees. This waiver system should be harmonised.

Similarly, some countries have implemented a waiver for the sponsor to purchase the IMP (investigational medicinal product) in non-commercial clinical trials, not other, and this initiative should be generalised.

In some countries, the insurance coverage for non-commercial trials is provided by the public health system, by the public hospitals or the university hospitals. This system should be implemented in all the EU member states, with the capacity to cover also investigator-driven trials sponsored by a foreign institution in a EU member state.

National competent authorities should provide free support to academic sponsor in SUSAR reporting and MedDRA coding.

Adaptation of the requirements should be allowed for marketed drugs regarding IMP dossier, and labelling. Alternative methods should be allowed to ensure traceability. Independence of academic trials should not be restricted by the need to ask the marketing authorisation holder to cross refer to an existing IMP dossier.

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?

1) *Interaction between ethics committees and competent authorities*

Various models have been implemented for the interaction between ethics committees and competent authorities: no interaction, a streamlined cross-talk, or a close cooperation in which the competent authority, not the sponsor, directly interacts with the ethics committee.

A guidance is needed to further define the respective tasks of ethics committees (protection of participants) and of competent authorities (assessment of the medicinal product), and how ethics committees and competent authority (either national, or a single EU competent authority) should cooperate in the clinical trial application process and during the conduct of the trial (for instance the model of a direct communication between the competent authority and the ethics committees, resulting in a one stop-shop system for the applicant that interacts only with the competent authority, has to be further discussed). This could reduce redundant work and increase clarity and responsibility.

2) *SUSAR reporting to ethics committees*

SUSAR reporting to ethics committees and to investigators is a major issue raised by ethics committees, investigators, and sponsors. We consider that an improved and streamlined communication between ethics committees and competent authorities could help solve this issue. SUSARs and AER should be reported by the sponsor only to the competent authority, while ethics committees and investigators could have access upon request to the data collected by the competent authority. In addition, a workshop should help discuss how best to make information on risk and benefit also available to participants in order to ensure the long-term validity of the informed consent.

3) *Information on national and EU requirements*

Information on national and EU requirements for clinical trial authorisation should be available, in English, to sponsors and investigators through a dedicated and updated website (at EMEA, or DG SANCO ?), and a helpdesk should be developed to support sponsors in multinational studies.

In addition, electronic documents (.pdf), not only paper documents, should be authorised for clinical trials application and submission to ethics committees.

4) *Investigational medicinal product (IMP) definition*

In the current guidance, only some background treatments are considered as IMP, and this requires case-by-case examination leading to divergent interpretation.

A simple and unambiguous definition of IMP should be provided. This is of particular importance for academic trials, as this has an impact on labelling and traceability, on SUSAR reporting, and as in some countries the academic sponsor still has to purchase the IMP.

5) *Definition of substantial amendments*

The definition of substantial amendments is open to varying interpretation resulting in different status across the EU member states.

A guidance should provide unequivocal definition.

6) *GMP (good manufacturing practice) requirements for bioterapy*

There is a need to harmonise the requirements for GMP manufacturing of biopharmaceutical products.

7) Education and training of investigators, nurses and other specialised staff

A guidance should be developed for education and training for investigators and staff in clinical trials, with accreditation of educational programmes. Continuous education of investigators and staff should be promoted. The issue of a qualification for investigators and staff should be discussed during a workshop.

8) Methodological assessment by ethics committees and competent authorities.

The competent authorities and ethics committees play a critical role in controlling the methodology of the protocol and in reducing the risk of errors – risk of design errors, risk of random errors ('play of chance'), risk of systematic errors ('bias'). There is currently a lack of quality assurance requirements and accreditation ensuring that the methodological review of protocols is adequately performed.

Clinical trials methodology should be part of guidance documents, quality assurance, and accreditation processes for ethics committees and competent authorities.

What should a new legal framework look like?

- 1) A **single and comprehensive legislation (directive and/or regulation) covering all clinical research** should be prepared, ensuring **adequate and equivalent protection of participants in any biomedical research in the EU**.

All the biomedical research on human beings, with or without health products, interventional or observational, should be covered by a single, legislative framework prepared under the umbrella of DG SANCO with the contribution of DG Research and DG Enterprises. In order to ensure harmonisation, a Regulation would be preferred to a Directive (whenever possible).

- 2) facilitating high-quality clinical science in the EU and **protecting the participants according to the risk associated to the category of study** (not according to its 'commercial' or 'non-commercial' objective).

Categories of research should be carefully and unambiguously defined, each being associated with regulatory and quality requirements adapted to the risk (instead of adaptation to 'non-commercial trials'). In turn, support should be provided to public institutions acting as sponsors in clinical research (possible co-sponsorship, support to MedDRA coding and SUSAR reporting, information and helpdesk on regulatory requirements, public insurance coverage, waiver of purchasing the IMP, development of the clinical research infrastructure). Workshops are needed to reach an agreement on the definition of, and borders between categories of research, the associated risk, and the resulting requirements.

- 3) with **centralised assessment by a single competent authority** (at least for multinational trials).

Instead of duplicating efforts, assessment of the health intervention should be conducted by a single agency (either centralised, or specialisation of the national competent authorities in a given type of health product, or mutual recognition).

- 4) with **accredited and co-ordinated ethics committees**.

Implementation of a quality assurance and accreditation system, and of an EU coordination under the responsibility of DG SANCO, leading to harmonised training and practice.

5) with clear guidance on their **respective roles**, and on the harmonised **interaction** between **ethics committees and competent authority**,

The national ethics committees should protect the participants in every category of clinical research, whereas the competent authority should assess the health intervention (including a health product if any), using a streamlined and harmonised procedure for interaction between both.

6) and promoting **trust, transparency and optimal use of data** in clinical research through open study registration, study reporting, and data sharing.

A clinical trial registration tool, in line with the requirements of the WHO international clinical trials registration portal (ICTRP) and of the ICMJE (International Committee of Medical Journal Editors) is lacking in the EU. The new EU legislation should state that data from the EudraCT database (and/or equivalent) will be used to build a public EU clinical trial register for all interventions (open access to information from EudraCT is already planned in the paediatric regulation). In addition, the EU should take advantage of this registration tool to give open access to study reporting, and to create a repository for anonymised clinical trial data.