Academic, hospital and charity sectors' comments on amendments adopted by the European Parliament's ENVI committee on the Clinical Trials Regulation

August 2013

We welcome the ENVI committee's work to improve provisions in the Clinical Trials Regulation to ensure that the final legislation is proportionate and facilitates the efficient conduct of clinical trials for patient benefit.

As a community we believe that significant progress has been made compared to the current Directive. However, there are issues that still need to be addressed before the Regulation is passed. This document is an analysis of key amendments passed by the ENVI committee in its 7 July 2013 report "on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC."

We make recommendations on possible revisions that will ensure the safe, efficient and transparent operation of clinical trials in Europe.

Key priorities for consideration in the trilogue negotiations

- The Regulation should continue to define which trials fall within its scope as opposed to defining which studies fall outside it. **We therefore oppose amendment 62 (Article 2**).
- The scope of low-risk clinical trials should not be reduced. The definition of normal clinical practice should be left for Member States to define. **We therefore oppose amendments 12 and 58 (Article 2).**
- The Regulation ensures that robust ethical review is part of the authorisation process. Ethical considerations should remain the responsibility of Member States and **we therefore oppose amendments 5 and 22 (Recitals 6 and 12).**
- We welcome the additional measures to promote transparency, but **amendments 191, 194 and 223 should be opposed** to ensure the proposals remain achievable and proportionate (Articles 33, 34 and 55).
- We support moves to introduce greater proportionality to monitoring and safety reporting introduced through amendments 198, 202, 209 and 288, and believe that these will support the efficient running of trials while maintaining patient safety (Articles 33, 39, 41 and Annex III).

This briefing considers key issues according to the order of chapters in the Regulation:

Chapter	**Relevant amend-ments**	**Relevant Recitals**	**Relevant Articles**	**Relevant Annexes**
Chapter I: General provisions	**12, 58, 61, 62**	**9**	**2**	
Chapter II: Authorisation procedure for a clinical trial	**5, 7, 22, 119, 122, 271**	**6, 8, 12**	**8**	**I**
Chapter V: Protection of subjects and informed consent	**158, 160, 162**		**28**	
Chapter VI: Start, end, temporary halt, and early termination of a clinical trial	**191, 194**		**33, 34**	
Chapter VII: Safety reporting in the context of a	**198, 199,**		**37-41, 50**	**III**

clinical trial	**201, 202, 207, 209, 219,288**			
Chapter VIII: Conduct of trial, supervision by the sponsor, training and experience, auxiliary medicinal products	**223**		**55**	
Chapter XIII: Supervision by Member States, Union inspections and controls	**19, 237, 242**	**10b(new)**	**74, 75**	
Chapter XIV: IT Infrastructure	**244, 246**		**77, 78**	

Chapter I: General provisions

Normal Clinical Practice (Recital 9 c (new))

The inclusion of the concept of normal clinical practice proposed by the Commission gives flexibility for Member States to determine what could be considered a low-intervention trial and which trials could benefit from risk adaption measures such as monitoring. However the recommendation in amendment 12 for the Commission to set guidance narrows the definition of normal clinical practice and therefore restricts the potential benefit of the proposed risk-based approach.

Oppose amendment 12.

Definition of 'Clinical trial' (Article 2 – paragraph 2)

We believe that certain types of studies that do not pose additional risk to patients should be removed from the scope of the Regulation. Studies falling outside the remit of the Regulation would still be subject to national ethical processes and robust scientific peer review

It is the study design, rather than the nature of the product, which often means a study is deemed to be a clinical trial. For example, the process of randomisation (Article 2 – paragraph 2 – point d) or the addition of any diagnostic or monitoring procedures (Article 2 – paragraph 2 – point e) cause even an authorised drug used within the terms of its marketing authorisation to be included in the scope of the Regulation. The additional monitoring and reporting requirements that are introduced when a study is considered a trial are not necessary or proportionate for studies of medicinal products being used in normal clinical practice.

We therefore suggest a more meaningful way to define the scope of the Regulation is through an amendment to ensure that routine low risk procedures, such as collecting an additional blood sample or blood pressure measurement, should not, of themselves, mean that a study falls within the scope. We propose the following amendment for consideration:

Proposed amendment:

Article 2 – paragraph 2 – point e

diagnostic or monitoring procedures **pose more than minimal additional risk or burden to the safety of the subject compared to normal clinical practice.**

Definition of 'low-intervention clinical trial' (Article 2 – paragraph 3)

Impact of intervention

Amendment 58 proposes that the definition of "low-risk trials" should include "Given the nature and extent of the intervention, can be expected to have only a very small and temporary or no impact on the subject's health."

The amendment would exclude many commonly used and well understood treatments from the low-risk clinical trial category. For example, in oncology almost all well-understood, licensed treatments are likely to have significant impacts and associated side effects on patients. Therefore this amendment does not support a proportionate approach to regulation.

In order to further develop new uses of established treatments – which may have significant but well understood health implications – we recommend that the sentence associated with 'very small and temporary or no impact' should be deleted from amendment 58.

Oppose amendment 58.

Use of placebo

We strongly support amendment 61 which allows trials to meet the definition of "low intervention" (or low risk) when placebo is used without increasing risk compared to normal clinical practice.

Support amendment 61

Definition of 'Non-interventional study' (Article 2 – paragraph 4)

A significant advantage of the Commission's proposals for the Regulation is that it positively defines what is deemed to be a clinical trial, as opposed to the existing Directive which defines only what is excluded from the scope. This means that studies which are not defined as trials in the Regulation automatically fall outside of the scope of the legislation.

An attempt to define criteria for a non-interventional study in amendment 62 will create legal uncertainty and confusion, for example when a study does not fall within the definition of non-interventional study (amendment 62), but also fails to fall within the definition of a clinical trial (Article 2). To ensure there is no conflict between the definitions, they would need to be perfectly complementary, in which case the definition of non-interventional study becomes redundant.

Oppose amendment 62.

Chapter II: Authorisation procedure for a clinical trial

No further extension to timelines

We welcome the Committee's decision not to significantly extend the timelines in the legislation. We strongly urge that the timelines in the Commission's proposal are maintained in order to keep Europe's trial set-up time competitive and to ensure the swift approval and reporting of trials.

No further action needed

Co-ordinated part I assessment (Recitals 6 and 12)

We believe that ethical review must remain the responsibility of Member States because of the different legal frameworks and cultural approaches to ethical review between Member States. This is the approach taken in the Commission's proposal.

We are concerned by amendments 5 and 22 that seek to bring ethical opinions within the scope of the part I assessment (which covers aspects of clinical trials that can be jointly assessed by Member States). Including these would mean that a dispute between Member States over an ethical issue could prevent a trial from being approved in all other Member States involved.

Currently there is no co-ordination or harmonisation of ethical committees in Europe therefore meaning a joint decision would be difficult to achieve. We therefore believe that ethical consideration should remain at the Member State level, as there may be specific contexts for trials in differing environments that individual Member States are best placed to judge. However, developing guidance for shared, best practice, training and accreditation in EU countries should be considered.

Oppose amendments 5 and 22. The Commission's original text should be restored.

Tacit Approval (Recital 8)

We support the Committee's intention to maintain tacit approval as an incentive for Member States to adhere to timelines.

Support amendment 7

Decision on the clinical trial (Article 8)

Involvement of Commission in arbitrating disputes

We do not believe the Commission should have a role in arbitrating on disagreements between Member States for Part I of the assessment and we therefore oppose amendment 119. This is because the

legislation does not set out what expertise the Commission should seek in order to arbitrate over disputes between Member States. We question whether the Commission would have the robust scientific and regulatory knowledge needed to support the decision.

Amendment 119 allows considerations other than normal clinical practice or infringement of national legislation to lead to Member States refusing to participate in trials. We do not support this as we consider that the Commission's original text was balanced in ensuring that joint approvals were streamlined. This amendment could result in the fragmentation of the approvals process, creating a burdensome system similar to that which has operated under the current Directive.

Oppose amendment 119.

Appeals process

A formal system allowing Sponsors to appeal against the negative assessment of Part II of the application is welcome.

Support amendment 122

Statistical analysis plan (Annex I)

In the process of developing a trial, a full statistical analysis plan would not available at the application stage as the plan is refined during the period of the trial. It is therefore not practical to ask for the plan at this stage. Amendment 271 should be revised to make clear that the protocol only needs to include an outline rather than a full statistical analysis plan. This would be available at application and registration stage and would be sufficient to ensure transparency in relation to planned trial and analysis.

Revise amendment 271

Chapter V: Protection of subjects and informed consent

General rules (Article 28)

Means to gather consent

We welcome the amendment that enables consent to take place through a range of suitable mechanisms and is not restricted to situations where there has been a patient/clinician interview. This will allow for a more adaptive design of trials and could help with the operation of much larger trials. However, we question the criteria laid down in amendment 160 that intends to ensure a patient's full understanding of the trial by means of an interview, since this undermines the intention of amendment 158.

Support amendment 158. Oppose amendment 160.

Reuse of data

Amendment 162 – which would require that consent forms are written in a manner to permit the reuse of data – is a positive step to ensure that data can be reused for the wider public benefit.

Support amendment 162

Chapter VI: Start, end, temporary halt, and early termination of a clinical trial

Notification of the start date of the clinical trial and of the end of the recruitment of subjects (Article 33)

Amendment 191 requires the start and end dates of recruitment to a clinical trial to be reported before a trial begins. This fails to take into account the nature of recruitment. There may be numerous reasons why the start or progression of recruitment is delayed. In addition, recruitment is unlikely to be completed by a specified date because it depends how long it takes to identify and recruit enough eligible patients. Therefore it is not possible for the Sponsor to adhere to this amendment.

Oppose amendment 191.

End of the clinical trial, early termination of the clinical trial (Article 34)

Requiring that data be submitted after a 12 month halt of a trial does not take into account legitimate reasons – such as supply shortages of the Investigational Medicinal Product (IMP), delays to recruitment, or staffing issues – that can halt a trial. We therefore believe there should be a Member State assessment following 12 months of temporary halt. At this assessment a decision should be taken on whether the trial outcome is considered to be early termination, in which case data must be submitted, or whether data can be held by the Sponsor until the trial restarts.

Review amendment 194

Chapter VII: Safety reporting in the context of a clinical trial

Reporting of adverse events and serious adverse events by the investigator to the sponsor (Article 37)

We welcome the proposals that low-risk (or low intervention) trials should follow established pharmacovigilance rules for reporting serious adverse events, as opposed to the system set out in the legislation. This amendment means that trials designated low-risk (low intervention) have an additional element which is risk adapted, this will allow trials to run more efficiently while maintaining patient safety.

Support amendment 198

Reporting of suspected unexpected serious adverse reactions by the sponsor to the Agency (Article 38)

Clinical trials are designed with the expectation that the IMPs being tested are the focus of the trial reporting. Therefore it is not reasonable to assume that suspected unexpected serious adverse reactions to auxiliary medicinal products (AMPs) should be reported in addition to IMPs. Amendment 199 appears to contradict the risk based approach taken in Amendments 198 and 201.

Oppose amendment 199

Annual reporting by the sponsor to the agency (Article 39)

Exemption from annual reporting for medicines used within their licensed indications or in standard use

We support the principle underlying amendment 201, which allows for further risk adaption for safety reporting. Medicines used within their licensed indications or in standard use outside their licensed indication would not need to produce annual safety reports. The amendment also allows for a single report for trials where multiple IMPs are being used in combination which would greatly benefit many trials, especially in oncology where treatment is made up of a combination of IMPs.

However, amendment 201 as currently drafted is very unclear and appears to suggest that products without marketing authorisations would not have to produce annual safety reports, which is a concern.

Revise Amendment 201:

Where a trial has not been designated low-risk the sponsor shall submit annually by electronic means to the Agency a report on the safety of each investigational medicinal product - or of all the investigational medicinal ***products - used in a clinical trial for which it is the sponsor.***

Single safety report

We welcome clarification that a single safety report is needed for multiple IMPs, this greatly reduces the reporting requirements for academic sponsors.

Support amendment 202

Reporting to ethics committees (Article 40)

Amendment 207 creates a potentially burdensome requirement for ethics committees to be involved in the assessment on SUSARs. Under the current Directive there is a requirement for adverse events to be reported to ethics committees and the issues associated with this were discussed in the Academy of Medical Sciences' review of regulation and governance published in 2011, as follows:

> "Reporting of both SUSARs and ASRs must be made to the relevant ethics committees in addition to the National Competent Authority (NCA). The National Research Ethics Service (NRES) highlights that there is widespread agreement among ethics committees in Europe that these obligations add no value to the monitoring of a trial because the information is already collected by the NCA. In the UK for example, RECs do not act on the safety information they receive. Instead, a Memorandum of Understanding between NRES and the UK's NCA ensures that NRES will be informed of any significant changes to the IMP's safety profile."[1]

Amendment 207 would be a step backwards in terms of proportionate reporting without providing any additional benefits in terms of patient safety.

Oppose amendment 207

Annual reporting by the sponsor marketing authorisation holder (Article 41)

We welcome the inclusion of Amendment 209 that requires submission of annual reports to the Agency as opposed to each marketing authorisation holder of an IMP. The Commission's text could have caused severe difficulties for trial sponsors.

Support amendment 209

Other reporting obligations relevant for subject safety (Article 50)

The concept of competent body has been removed from the Regulation to allow Member States to organise their internal approval process as they see fit. We do not believe that this concept should be reintroduced.

Oppose amendment 219

Safety reporting following close of trial (Annex III)

We agree with amendment 288 that following the end of a trial adverse events should only be reported where they are judged to be related to the IMP.

Support amendment 288

Chapter VIII: Conduct of trial, supervision by the sponsor, training and experience, auxiliary medicinal products

Archiving of the clinical trial master file (Article 55)

We question the practicality and utility of indefinitely holding trial master files.

The master file is the archive of all the patient records and information related to the trial, much of it on paper. A requirement for the master file to be available electronically would not currently be achievable in most health systems and would seriously damage the ability of sites to run trials. While electronic master files may be an option for the future, this should not be mandated in legislation.

[1] The Academy of Medical Science, *A new pathway for the regulation and governance of clinical research*, (2011) p.51

While the Commission's proposal to hold the master file for at least 5 years is too short, indefinite archiving could pose a significant undertaking for either a Sponsor or an EU database. A proportionate approach needs to be found with a reasonable timeline, for example 20 or 25 years.

Revise amendment 223.

Chapter XIII: Supervision by Member States, Union inspections and controls

Member State inspections and Union controls and Union Inspections (Articles 75 and 76 and Recital 10 b (new))

Amendments 19, 237 and 242 exempt non-industry sponsors from fees associated with running clinical trials. We welcome the principle behind this. However, it is important to ensure that Member State regulatory agencies are properly resourced in order to carry out swift and robust assessments of applications and safety monitoring. This should be taken into consideration when assessing whether to take forward this amendment.

Review amendments 19, 237 and 242

Chapter XIV: IT Infrastructure

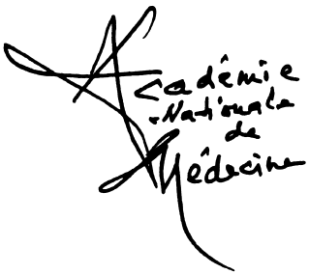
The community is concerned whether the EU Portal and database will be operational by the time the Regulation comes into force. We would welcome further clarity from the Commission on the progress of the portal. However, we do not believe that amendments 244 and 246 that would place the portal in the jurisdiction of the EMA are particularly useful in resolving this issue (Articles 77 and 78).

We welcome the section in amendment 244 that require that submission and reporting into the new IT infrastructure should not duplicate existing IT reporting mechanisms.

Review amendments 244 and 246

For further information please contact Daniel Bridge (daniel.bridge@cancer.org.uk, 0203 469 8153)

Supporting organisations



KONINKLIJKE NEDERLANDSE
AKADEMIE VAN WETENSCHAPPEN