

Network of Coordinating Centres for Clinical Trials (KKS-Network), Germany and the German Association for Hematology and Medical Oncology e. V. (DGHO)

Comments on the

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

Committee on the Environment, Public Health and Food Safety

The KKS-Network, which is the German network of academic clinical trial units at universities / university clinics, and the German Association for Hematology and Medical Oncology welcome the proposal of the European Commission for a regulation on clinical trials on medicinal products for human use. A lot of the changes proposed to the regulatory framework will ultimately lead to a more stringent and less bureaucratic application and authorisation procedure. However, there are areas in the proposal that could be improved and/or need clarification. We therefore welcome many of the amendments proposed in the report of the Committee on the Environment, Public Health and Food Safety and proposed by the other Committees involved in the discussion process which form part of the report issued in June 2013. But there are also amendments in the report which are of concern to academic clinical research. We therefore herewith would like to address those concerns. We will be focusing on those amendments or original parts of the proposal that present a problem or concern for academic clinical research in Germany. We would be very grateful if our considerations could be taken into account in the ongoing discussions between EU-Parliament, European Council and the European Commission.

Key priorities for consideration in the Trilogue negotiations:

- Timelines (including the timelines for response of the sponsor) for the assessment procedure should be prolonged in a more substantial way than currently proposed to ensure a high quality coordinated procedure.
- The Regulation should continue to define which trials fall within its scope as opposed to define which studies fall outside it.
- The scope of low-intervention clinical trials should not be reduced. This is especially important for clinical trials in minors, where treatment often is outside the marketing authorisation, but is standard therapy in a given Member State. The definition of normal clinical practice should be left up to the Member States.
- The process of patient information and to obtain informed consent should be constructed in a way that ensures patient protection, is practical and offers flexibility for further research. Informed consent should be mandatory for all clinical trials.
- The Regulation should ensure that robust ethical review is part of the authorisation process. Ethics committee approval should be mandatory in both parts of the approval process (overall decision and within the Member States). Safety reporting is a key to a continued benefit-risk-evaluation for the conduct of the clinical trial. The reporting to the EudraVigilance database should therefore be conducted by those who have the technical capabilities and the reporting to the database should be focused on events where relationship is assumed with the IMP.
- We very much welcome that the European Commission has introduced a national indemnification scheme for clinical trials not aiming at marketing authorisation. This will help academic clinical trials and we therefore strongly plea not change this concept during the ongoing discussion.

General comments:

In the text of the European Commission and the proposed amendment, reference is made to the 2008 version of the Declaration of Helsinki. This should be changed to “the most recent version of the Declaration of Helsinki” to avoid conflicts.

Chapter I – General provisions – Article 1 – Article 3

PASS / PAES to be excluded from the risk-based approach

Article 2 – paragraph 2 – point 2 – point e a (new), Amendment No 57 ENVI

For clarity it should be added that the PASS or PAES mentioned here are only those clinical trials which are part of a conditional marketing authorisation granted by the competent authority.

Normal Clinical Practice

Recital 9 (c) new, Amendment No 12 ENVI

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 adaptation measures. 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. *We would recommend sticking with the text of the European Commission and to oppose amendment 12 ENVI*

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.

It is the trial 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 manufacturing 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 clinical 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 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.**

Change wording from low-intervention to low-risk or minimal risk trials / Impact of intervention

Recital 9, Amendment No 9 ENVI, Amendment No 5 ITRE, Amendment No 3 IMCO

Article 2, paragraph 2 – point 3- introductory part, Amendment 58 ENVI, Amendment No 29 IMCO

Article 2, paragraph 2 – point 3 – point (c), Proposal of the European Commission

We are not supportive of changing the wording from low-intervention to low-risk or minimal risk. The concept of low-intervention refers to the additional intervention as compared to

“normal clinical practice”, i.e. to the risk a patient would run if treated outside a clinical trial, and is therefore preferable to the concept of “low-risk”. We are not supportive of the term “minimal risk trial”. Minimal risk (see Amendment ITRE) is used in the context of clinical trials with minors or with subjects not capable of providing informed consent. For a clinical trial as such it is difficult to state that it will be only minimal risk; because of the indication and the medicinal product needed to treat the indication the risk might per se be more than minimal.

Amendment 58 ENVI and Amendment No 29 IMCO propose that the definition of “low-risk trials” should include “a clinical trial, which, 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 wording of this amendment is unrealistic and would exclude many treatments used in normal care from the low-risk clinical trial category. For example, in oncology or HIV even well-understood, licensed treatments are likely to have significant impacts and associated side effects on patients, which might be more than temporary.

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 ENVI

Use of placebo

Article 2 – paragraph 2 – point 3 – subparagraph 2 (new), Amendment No 61 ENVI

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

Support amendment 61 ENVI

Definition of ‘Non-interventional study’

Article 2 – paragraph 4, Amendment No 62 ENVI

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 ENVI

Definition of principal investigator / coordinating investigator

Article 2 – paragraph 2- point 14 – European Commission proposal

Article 2 – paragraph 2 – point 14 a (new), point 14 b (new); Amendments No 69, No 70 ENVI

In the legislative text the European Commission proposal focuses on the concept of one responsible investigator per site. To make this absolutely clear we would recommend changing Article 2 – paragraph 2- point 14 to

(14) “investigator”: the individual responsible for the conduct of a clinical trial at a clinical trial site

The principal and coordinating investigator which are introduced by Amendments 69 and 70 ENVI are not mentioned in the regulation. We are not supportive to introduce definitions which are otherwise not used within the regulation; if the definitions would be introduced,

this would require clear, distinct differentiation of responsibilities throughout the legislative text and all accompanying texts. In our view those definitions are not necessary as there is a reference made to ICH E6 in the text. ICH E6 does only say that the investigator responsible at a trial site may be called principal investigator, but this does not necessarily have to be the case. In practice, the amendment bears the risk that tasks are not adequately defined and assigned to the different roles / persons involved in the conduct of the clinical trial at a trial site. This has been the case in the past and has led to different interpretations. Furthermore, if there are no special tasks assigned to a principal or coordinating investigator in the regulation, it is not necessary to define the role.

Delete amendments 69 and 70 ENVI

Including a definition for adverse reactions:

Article 2 – paragraph 2 – point 28 a (new), Amendment No 19 ITRE

A definition of adverse reaction is not needed (already defined by reference; see Proposal for a regulation, Article 2: reference to Article 1 (11) of Directive 2001/83/EC). Furthermore, adverse event and adverse reaction have different meanings.

We propose to delete amendment 19 ITRE

Chapter II / III – Authorisation procedure for a clinical trial and substantial modifications of a clinical trial – Article 4 – Article 24

Timelines

We would very much recommend prolonging all timelines in the assessment process (including response times for sponsors) in a way that ensures a thorough and cooperative assessment procedure. To prolong timelines by 2 days as proposed in the report is not felt to be enough, especially as all timelines are based on calendar days. Not only competent authorities and ethics committees, but following current experiences at least academic sponsors might also have difficulties in adhering to the timeframes given. In cases the sponsor is not able to respond to requests within the timeframe given, the application would be considered as withdrawn. This would not be in the interest of academic research.

A reasonable prolongation of timelines is in our view justified when taking into account set-up times for a clinical trial; in the vast majority of cases the time from the first idea / hypothesis for the trial until application for authorisation lasts several months. Furthermore, the decision at the end of the process would be in most cases a European Decision.

Authorisation including approval (positive opinion) of an ethics committee / Explicit mentioning of Ethics Committees:

Several amendments to recitals and articles 4, 8, 15, 23

We support amendments which aim to clarify that the vote of independent ethics committees form part of the assessment procedure for clinical trials. But the role of the ethics committees should not be restricted to part II of the assessment (amendment No 79 ENVI). A clinical trial which is not designed properly can also lead to ethical concerns. General ethical aspects (i. e. ethical aspects which are not of intrinsic national nature) of a clinical trial can not be excluded from the assessment in Part I and those aspects can not be restricted to the ethics committee of the reporting Member State. A positive opinion of the EC should always be mandatory to start a clinical trial, this is in our view not sufficiently covered by the words “may examine”.

We strongly recommend deleting amendment 79 ENVI

There are aspects of intrinsic national nature. This should be acknowledged, and those aspects should not be the reason why a clinical trial can not be conducted in the other

Member States of the European Union. But the exchange of views and the discussion of those aspects should be encouraged.

Furthermore, when amending the proposal to explicitly include the wording ethical committee into the regulation, it is important that the assessment procedure of CA and EC is run in parallel and that the approval / positive opinion of the EC constitutes part of the single decision per Member State. Additionally, it should be clearly stated that there need to be objective grounds for non-approval. In our view, it would be preferable to state the grounds, but not the body which would not approve the trial.

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 ENVI. We are also concerned that 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 Directive.

Oppose amendment No 119 ENVI

Chapter IV – Application dossier – Article 25- Article 27

Reference to data from previous trials

Article 25 – paragraph 4, Amendment No 148 ENVI

We support the amendment in principle, but it might not go far enough as reference might also be made to clinical trials conducted prior of the entry into force of Directive 2001/20/EC. Therefore it is suggested that this is also taken account of.

Proposed requirement for retrospective registration of clinical trials

Recital 20, Amendment No 29 ENVI, Amendment No 15 IMCO

Article 25 – paragraph 6; paragraph 6 – subparagraph 1 a (new)

Amendment No 151, 152 ENVI

It might very well be that the data used to support a clinical trial are data from clinical trials conducted before 2005. In such a case it is likely that the clinical trials have not been registered in a registry. A retrospective registration of clinical trials would pose high administrative burden especially on academic clinical research. The persons responsible for the trials conducted might not be available any longer and there might be no institution responsible instead. It would not make sense to exclude important results only because no retrospective registration can take place. Alternatively, data from clinical trials conducted before 2005 which have been published in a peer reviewed journal should also be acceptable. The reliability of the data is not enhanced by retrospective registration.

We suggest deleting the proposed amendments.

Chapter V – Protection of subjects and informed consent – Article 28 - 32

Obtaining informed consent

Article 28 – paragraph 1 – point d, Amendment No 78 IMCO

Article 30 – paragraph 1 – point b, Amendment No 170 ENVI, Amendment No 81 IMCO

Informed consent from a subject should be obtained from the investigator or a member of the investigating team who is a physician. The amendments proposed would introduce hurdles to the conduct of clinical trials.

Oppose amendments No 158 and 170 ENVI and amendments No 78 and 81 IMCO

Test of full understanding

Amendment No 160 ENVI is asking that “the prior interview with the investigator or a member of the investigating team in order to obtain the subject’s informed consent shall include a test of full understanding on the part of the subject and/or his or her de facto representative by, for example, asking them to summarize the information which they have received”. We agree that the physician who obtains informed consent has to ensure, that the subject did understand all the implications of the clinical trial, the potential risks and benefits and obligations – but the way he ensures this should be left to the physician who will decide according to the subject and the situation. If the requirement of a “test of full understanding” is part of the legislative text, then this would have to be conducted in a way it can be proven. It would be difficult to get a consensus on how this could be reached as this would be dependent on the capabilities of the subject involved.

Oppose amendment 160 ENVI

Principle of broad consent:

Article 28 – paragraph 2 a (new), Amendment No 162 ENVI, Amendment No 48 ITRE

We are very supportive of amendments No 162 ENVI and amendment No 48 ITRE that include the possibility for broad consent, so that the data obtained in a clinical trial can be used later on to resolve research questions which have evolved with time – this is a positive step to ensure that data can be reused for the wider public benefit

Support amendment 162 ENVI

Revoking informed consent – use of data obtained until the date consent is withdrawn / proportionate risk in clinical trials in emergency situations

Article 28 – paragraph 3, Amendment No 163 ENVI

Article 32, paragraph 2 a (new) Amendment No 190, ENVI, Amendment No 92 IMCO

These amendments constitute a major concern. From the point of view of statistical analysis, it would compromise the whole clinical trial and the data obtained so far, if data sets need to be excluded from the analysis because consent was revoked later on during the trial or – with regards to clinical trials in emergency situations – not obtained for the continued participation in the clinical trial once the patient or his/her representative would be able to provide consent. The results of the trial may be heavily biased by retrospective data exclusion, and the reliability of the data of the whole clinical study may be compromised. This would possibly lead to situations with no benefit at all for all the subjects / the group of subjects who participated in the trial, as statistical power has not been reached or the results are biased and not interpretable. This would make the conduct of the clinical trial unethical retrospectively. The possibility to withdraw consent for the use of data obtained should therefore be restricted to the use of any data from the time of denial of consent onwards. This should be clearly stated in the regulation.

Article 32, paragraph 1 letter (e) Amendment No 190 ENVI

Clinical trials in emergency situations do not always pose only minimal risk to the patient,

and no participation in the clinical trials could very often mean a higher risk for the safety of the patient than participation. The risk for the subject should therefore be proportionate to the possible benefit. Amendment 190 ENVI does take account of this in the proposed change for letter (e). We are very supportive of this part of the amendment, as the original text of the European Commission would still have meant that a lot of important clinical trials could have not been conducted.

Delete amendment 163 ENVI and amendment 92 IMCO

Rephrase amendment 190 ENVI.

Clinical trials without prior informed consent

Recital 24, Amendment No 34 ENVI

Article 29 – paragraph 3 a (new), Amendment No 167 ENVI

These amendments constitute a major concern. We can not foresee any clinical trials justifying that no informed consent is obtained from the subject. The only situations which do justify starting without PRIOR informed consent are emergency situations, but in those cases consent will be asked for as soon as possible from the subject or the subjects representative.

Apart from this general concern we do not understand the purpose of the amendment and in our view the amendment in itself is inconsistent / contradictory (3a and 3 e/3f/3g).

Oppose amendments No 34 and 167 ENVI

Requirement for informed and express consent for minors who are 12 years or older

Article 31 – paragraph 1 – point a a (new), Amendment No 176 ENVI

Article 31 – paragraph 2 – point 1 a (new), Amendment No 185 ENVI

In our view it is not sensible to provide an age from which on full and express informed consent of the minor should be obtained. The important criterion is the capability of the minor to provide full consent. This judgement should be left to the investigator.

Delete amendments 176 and 185 ENVI

Necessity of research in minors

Article 31 – paragraph 1 – point 1 e, Amendment No 179 ENVI

We support the point proposed by the European Commission and do not understand the rationale of ENVI to delete this point.

Oppose amendment No 179 ENVI

Replication of trials based on the same hypothesis and age-appropriate formulations

Article 31 – paragraph 1 – point 1 h c (new), Amendment No 183 ENVI

There may be a good reason for replicating a clinical trial, this needs justification but should not be excluded as such. With regard to using age-appropriate formulations: this should be of course an aim but it could not be so easy to reach as this could include testing of bioavailability, pharmacokinetics, pharmacodynamics. We would suggest not to state this as requirement.

Delete amendment No 183 ENVI

Chapter VI – Start, end, suspension, temporary halt and early termination of a clinical trial – Article 33 – Article 35

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

Amendment 191 ENVI 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.

Amendment 191 ENVI should be deleted or rephrased (anticipated dates to be provided)

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

Article 34 – paragraph 4, Amendment No 194 ENVI

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 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.

Rephrase amendment 194 ENVI

Chapter VII – Safety reporting in the context of a clinical trial – Article 36 – Article 43

Reporting of Serious Adverse Events from the investigator to sponsor, database and agency

Recital 26, Amendment No 10 ITRE

Article 37 – paragraph 2, Amendment No 52 ITRE

These amendments are a concern. Normally, the investigator is with regard to resources and technical possibilities not able to register and report serious adverse events to the agency and the database! As foreseen by the European Commission – and current practice - the investigator should report SAEs to the sponsor who should then report only such events which fulfil the definition of SUSARs electronically to the EudraVigilance Database and record all other serious adverse events in the CRF and in the annual safety report. The amendments would introduce a lot of double reporting

Delete amendments 10 and 52 ITRE

Electronic reporting of SUSARs / Reporting of SUSARs of auxiliary products

Article 38 – paragraph 1, Proposal of the European Commission

Recital 27, Amendment No 37 ENVI; Article 38 – paragraph 1, Amendment No 199 ENVI

Annex III – part 2 – point 7, Amendment No 289 ENVI

There might still be sponsors who are not able to report electronically. For those, it should be possible to report also in paper format.

Furthermore, the reporting of SUSARs of auxiliary products would include a lot of additional work for sponsors. For those products which are not an investigational product in the trial, normal reporting rules for those products should apply.

Additionally the meaning of „related to the sponsor“ requires clarification.

Oppose amendment No 199 and 289 ENVI, rephrase Article 38 of the proposal of the European Commission

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 ENVI

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 ENVI in the following way:

Where a trial has not been designated low-intervention the sponsor shall submit annually 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 ENVI

Reporting of efficacy defects of authorised investigational medicinal products

Article 39a (new), Amendment No 204 ENVI

We are not supportive of this amendment. Those defects, if noticed by the investigator, would constitute an adverse event and would need to be reported to the sponsor anyway. In addition, lack of efficacy is in most cases not detectable on a single case basis, but would be noticed in the statistical analysis of the clinical trial only.

Delete amendment 204 ENVI

Involvement of EC of the concerned Member States into the assessment of SUSARs

Article 40 – paragraph 2 a (new), Amendment No 207 ENVI

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. This has not proven effective and reasonable. The issues associated with this have for example been 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."

Amendment 207 would be a step backwards in terms of proportionate reporting without providing any additional benefits in terms of patient safety. The Ethics Committees should be informed instead when there is a change in the benefit-risk-ratio of the clinical trial.

Oppose amendment 207 ENVI

Annual reporting by the sponsor marketing authorisation holder

Article 41, Amendment 209

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 ENVI

Safety reporting following close of trial (Annex III)

Annex III – part 1 – point 4, Amendment 288 ENVI

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 ENVI

Registration of adverse events in the EU portal

Annex III – part 1 – point 4 a (new), Amendment No 64 ITRE

The sponsor has the obligation to record all adverse events, but to register all adverse events (not serious adverse events or SUSARs) in the EU portal would not make sense. Furthermore, safety reporting is via the EudraVigilance database.

Delete amendment No 64 ITRE

Chapter VIII - Conduct of the trial, supervision by the sponsor, training and experience, auxiliary medicinal products – Article 44 – Article 56

Handling of investigational medicinal products

Article 48 – paragraph 1 – subparagraph 2a (new), Amendment No 215 ENVI (in combination with Article 48 – paragraph 1, subparagraph 1)

The amendment would mean, that investigational products can only be received, stored, traced, administered, destroyed and returned by pharmacists or other persons legally authorised. This is not sensible (especially with regards to administration).

Delete amendment 215 ENVI

Reporting of Serious breaches

Recital 33, Proposal of the European Commission

Recital 33, Amendment No 41 ENVI, Amendment No 20 IMCO

Article 49, paragraph 1, proposal of the European Commission

Article 49 – paragraph 1, Amendment 217 ENVI

Article 49 – paragraph 2, Amendment 218 ENVI, Amendment No 107 IMCO

We are neither supportive of the text of the European Commission nor of the amendments proposed by ENVI and IMCO. We are supporting the principle of transparency including rules to support prevention of misconduct. But we anticipate problems with the reporting of serious breaches. First of all it seems to be necessary to clearly define serious breaches which need reporting (Article 50. paragraph 1, Amendment No 218 ENVI, Amendment No 107 IMCO are not felt to be specific enough) in order to assess this requirement. Will this information be publicly available, as this might then pose a problem with regards to the EU Charta on Fundamental rights? What would be the evidence needed? Normally, the task of the sponsor is to put corrective measures in place, if needed, the notification of breaches would be the task for inspections.

Delete Proposal for recital 33 and article 49, paragraph 1 of the proposal of the European Commission and amendments No 42, 217, 218 ENVI and amendment No 20 and 107 IMCO

Storage of the Trial Master File / Requirement to store the content of the trial master file for an indefinite period of time

Article 54 – paragraph 1, Amendment No 222 ENVI

The sponsor has the overall, ultimate responsibility for the clinical trial. It is therefore not adequate to propose that the sponsor or the investigator should keep the TMF. Only special parts of the trial documentation will remain with the investigator and form the investigator site file of the trial master file.

Furthermore, the contents of the TMF are defined (see e. g. ICH E6); a requirement for special und readable and easily searchable formats is not adequate.

Oppose amendment No 222 ENVI

Archiving of the clinical trial master file (Article 55)

Article 55 – paragraph 1 – subparagraph 1, Amendment No 223 ENVI

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. We would instead propose to archive the content of the clinical trial master file for at least 10 years after the end of the clinical trial and to electronically archive patient level data for a period of at least 50 years.

When looking at the justification of the amendment we find it more than reasonable that an inspection should have been completed within 10 years after the end of the trial, as – if there really has been misconduct – it would be in the interest of patients and society to know about this as early as possible. Furthermore, especially archiving for the proposed period of time at the investigator site is difficult and unconvertible.

Revise amendment 223 ENVI

Chapter XI – Sponsor and investigator – Article 68 - 71

Co-sponsorship

Article 69 – paragraph 2 – introductory wording, Amendment No 230 ENVI

We are of the strong opinion that there needs to be one sponsor responsible for central tasks of a clinical trial. In our view this should also – besides the tasks defined in article 69, paragraph 2 of the European Commission proposal – include central quality management and safety management. We therefore are especially not supportive of Amendment 230 ENVI to Article 69 – paragraph 2 – introductory wording. For some central tasks there should be only one sponsor having the oversight and responsibility.

Oppose Amendment No 230 ENVI

Chapter XII - Damage compensation, insurance and national indemnification mechanism – Article 72 – Article 73

The vast majority of academic clinical trials are aiming to improve and optimise existing therapeutic schemes. They evolve out of observations made during regular clinical practise. Their conduct is in the interest of patients and society, but also of health care systems.

To pay for a possible damage of patients participating in such trials should therefore be a national task. Data from the past have shown that the risk for subjects participating in the trials mentioned and therefore the financial risk for society is low. On the other hand, costs for insurance of patients participating in clinical trials are often very high and may prevent important clinical trials from being conducted, as academic clinical trials very often suffer from a shortage of financial resources. We therefore very much welcome that the European

Commission has introduced a national indemnification scheme for clinical trials not aiming at marketing authorisation, that should be free of charge for academic sponsors. This will help academic clinical trials. We therefore strongly plea not to change this concept during the ongoing discussions.

Support proposal of the European Commission

Chapter XIV – IT Infrastructure – Article 77 – Article 78

Set up and maintenance of the EU Portal / the EU-Database

Recital 51, Amendment No 46 ENVI,

Article 77 – paragraph 1, Amendment No 244 ENVI,

Article 78 – paragraph 1 – subparagraph 1, Amendment No 246 ENVI

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). Furthermore, it is not clear which financial implications this would have for academic sponsors.

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

Review amendments 46, 244 and 246 ENVI

Public access to detailed and summary raw data / Public access to clinical study reports held in the European database

Article 78 – paragraph 1 – subparagraph 2, Amendment No 57 ITRE

Article 78 – paragraph 7 a (new), Amendment No 253 ENVI

We are of the opinion that raw data should be made available on request for scientific reasons. But those data should not be stored in a database which is publicly accessible. We doubt whether patients without medical background will be able to make an informed decision about their health on the basis of detailed raw data or clinical study reports. We think there should be a differentiation with regards to which contents are searchable for whom.

Oppose amendment 57 ITRE, revise amendment 253 ENVI

Chapter XVI – Fees – Article 82 – Article 83

Waiver for fees for academic clinical trials

Recital 10 b (new), Amendment No 19 ENVI

We would very much appreciate a general waiver of fees for academic clinical trials.

Annex

Evidence for conducting the clinical trial

Annex I – part 4 – point 13 – indent 2, Amendment No 267 ENVI

We are not supportive with the current wording. It will not be possible to reference all existing evidence for several reasons, e.g.:

- how does one get to know whether the list is complete?
- what about pending publications (the evidence is there, but not available)
- this might change from day to day

The word “all” should therefore be deleted.

Revise amendment No 267 ENVI

Full statistical analysis plan - where possible

Annex I – part 4 – point 13 – indent 3 c (new), Amendment No 271 ENVI

In the process of developing a trial, a full statistical analysis plan is 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. At the time of the application of the clinical trial the protocol includes a description of the statistical methods (how the primary endpoint will be analysed) and the population to be analysed. More details and more specifications will follow before the analysis will take place. This is justified as there might be amendments to the protocol during the conduct of the trial which need to be taken account of as well as of the database and structure of the data.

Amendment 271 should be revised to make clear that the protocol only needs to include an outline statistical analysis plan, rather than a full statistical analysis plan. An outline statistical analysis plan 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 ENVI

Berlin, 22. October 2013