European Commission proposal for a Regulation on Clinical Trials (COM(2012) 369 final)

EPF Position Statement

February 2013

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Methodology of developing this position paper

EPF and its member organisations have provided extensive input into the debates around the revision of the clinical trials directive, including responses to several public consultations.[1] Based on this work and the priority issues identified by our members, a draft position paper was developed with input from EPF's Policy Advisory Group. The final version has been developed based on input from two rounds of member consultation and internal meetings. This position paper may be updated in the course of the legislative process, as necessary.

A. Introduction

EPF warmly welcomed the legislative proposal of the European Commission for a Regulation on clinical trials (COM (2012) 369 final), published in July 2012. Whilst directive 2001/20/EC – the Clinical Trials Directive – introduced some important provisions for the protection of patients participating in clinical trials, it has also led to an increased administrative burden and costs of clinical trials. The 25% decline in clinical trials performed in the EU, and the increase in the average delay for launching a trial by 90%[2], are deeply concerning.

[1] EPF's previous statements around clinical trials can be found here, here and here.

[2] Commission legislative proposal COM (2012) 369 final, Explanatory memorandum, pp. 2-3.

We would stress that the new EU clinical trials regulatory framework will be with us for many years to come. This is why it is vital to get it right. The Regulation should be forward looking, in order to address the change and evolution in science, and also in the way science is done. The latter includes much wider public transparency around research and research results and information, as well as an increasingly central role played by the patients. It is for the benefit of patients that clinical trials are conducted; it is the patients who voluntarily participate in research, and who ultimately bear the risks of doing so. The patient3 therefore must be at the centre of the clinical trials Regulation.

EPF calls for patient and civil society involvement to be embedded in all aspects of research, from the "idea" stage, priority setting of research topics, design of studies, through to the way the results of research are made available. Furthermore, EPF calls for equity of access for all patients and citizens to the "fruits" of innovation, which should address the current inequalities in health and currently unmet medical needs.

The European Commission's proposal for a Regulation introduces a number of major improvements to the current situation, which will help reduce barriers to the conduct of clinical trials in the EU and stimulate innovation. However, specific aspects of the Regulation can be improved upon. Below, we set out EPF's view on the main aspects of the proposal.

B. Key aspects relating to assessment of trial applications

1. Single electronic submission through EU portal

EPF welcomes the single submission, as this will reduce the administrative work of sponsors who would otherwise have to submit the same documentation to all the Member States separately. The single submission with its flexible geometry will enable even smaller sponsors with fewer resources (e.g. academics) to submit clinical trials applications, and can lead to more transparency and clarity for European patient community as a whole.

EPF recommends:

1) For multi-centred trials in small populations (such as in the case of rare diseases), the reporting Member State should integrate in its report all the existing expertise, which is by definition scarce and difficult to gather. Therefore, a way should be established to ensure that all the expertise coming from the relevant Scientific Committees of the European Medicines Agency (COMP, CAT and PDCO) is integrated, in order to ensure that the decision-making process is informed by all existing knowledge, from the application until the final authorisation stage.4 The consultation of an Expert Group could be the most constructive way forward, while keeping the flexibility of the system.

[3] Or a trial participant who is not a patient, such as healthy volunteers who participate in phase 1 clinical trials or trials in disease prevention such as vaccination.

[4] An example comes from the Netherlands, where a discussion around reimbursement for therapies on Pompe and Fabry disease has highlighted that that health insurers make their own judgments on the efficacy of the treatment, after a longer observation period of the drug being used, and they may come to a different conclusion than the EMA at the stage where marketing authorisation was granted. A larger database at EU level would be needed to have a clear impression on the efficacy of rare disease therapies.

2. Timelines for assessment

The timelines proposed by the European Commission are ambitious, but based on current best practice. EPF is in favour of speeding up assessment of trial applications, while this must not undermine the quality of the assessment. It is clear that Member States will need to make changes to their national systems in order to issue an approval within the time lines specified in the legislation. Effective collaboration and communication between the different bodies involved in assessment at the national level is essential.

EPF recommends:

2) EPF urges Member States to make the necessary adaptations to ensure compliance with timelines.

3. Coordinated assessment of trial applications

EPF welcomes the principle of coordinated assessment by the concerned Member States. It is critical to include in the joint assessment an evaluation of whether the clinical trial addresses issues identified as priority by patients. The protocol should describe the extent and nature of patient involvement in identifying the research topic, research questions and the overall trial design. Research applications that address unmet patient and public health needs should be prioritised in all EU calls for proposals under the research framework programme.

In the joint assessment it should also be assessed whether the trial population is reasonably representative of the population that will be later treated by the medicinal product. In particular, the trial participants should represent a balanced population in terms of age and gender. This will ensure that the impact of the drug on the whole target population, including possible adverse effects, is assessed during its development.

EPF recommends:

3) The assessment of the application for a clinical trial, when evaluating its relevance, should include an assessment of patient involvement in research priority setting. This should be described in the protocol. Applications with meaningful patient involvement and that meet patients' needs should be prioritised for funding under the EU funding programmes.
4) The trial population should be representative of the target population, and if this is not the case it should be justified and explained.

4. Single decision and qualified opt-out

EPF welcomes a single decision per Member State. Having a single reporting Member State simplifies and streamlines the procedure, and since the proposal obliges the reporting Member State to prepare the assessment in consultation with the other concerned Member States, this should promote closer collaboration.

Regarding the qualified opt out, EPF firmly believes that patients and the public have a right to know why a given Member State would refuse to participate in a clinical trial that is acceptable to the other concerned Member States. Therefore, the reasons for opt outs should be made public by the European Commission. EPF further calls for the reasons for opting out to be strictly limited, only include the two reasons included in the proposal, namely an existing national legislation concerning human or animal

cells, and that trial subjects would receive worse treatment in the trial than under normal clinical practice in that Member State. (In assessing the latter, we reiterate that patients' views must be sought as provided by Article 9.)

EPF is concerned that patients wishing to participate in a clinical trial involving advanced therapies forbidden under the national legislation of one Member State, would be deprived of access to the trial if the Member State refuses to participate. No patient should be deprived of the chance to be in a clinical trial – especially if this is a vital opportunity to access treatment when is no other option. EPF recommends that a provision allowing for cross-border access to clinical trials should be included in the proposed Regulation. The potential to apply Directive 2011/24/EU on patients' rights in cross-border healthcare in such situations should be explored.

EPF recommends:

5) The reasons for qualified opt outs should be made publicly available through the EU database.
6) Reasons for opting out of joint assessment should be strictly limited to include only the two reasons provided in the Commission's proposal.
7) Individual patient access to clinical trials should be facilitated, even when a Member State opts out.

5. Patient involvement in assessment of clinical trials

The Regulation introduces a requirement for patient involvement, applicable to both parts I and II of the assessment, as well as substantial modifications. EPF strongly welcomes this recognition of the central importance of patient involvement in research. This is crucial in order to ensure that the trial is relevant to patients' needs and to obtain an accurate risk-benefit assessment. Patients provide the information, and they ultimately manage the personal risks attached to trials. Patients therefore have a moral right to be involved in the way clinical trials are developed, managed and evaluated. Moreover, it has been demonstrated that patient involvement leads to better trial design and outcomes of trials.[5] It is extremely important that patients are involved throughout the process.

However, the wording of Article 9 is not sufficient in our view. The view of one patient is not enough, as it is difficult for one patient to represent the view of all patients in a clinical trial. In fairness and to give strength to the process, there must be at least two. Therefore, a support structure needs to be put in place. Guidelines are needed at EU level to define how patient involvement should be implemented, drawing upon existing good practice in this area and addressing the necessary capacity-building and the role of patient organisations.

Which patients?

EPF does not prefer the term "expert patient". EPF is concerned that using this term may imply that patient involvement may be made conditional upon a certain level of scientific knowledge. Although many patients are very knowledgeable about scientific issues, EPF stresses that the unique value of the patient perspective lies in the direct experience of a person living with a condition or disease. This perspective should not be lost by introducing requirements for expert qualifications into the legal text.

[5] EPF's statement on clinical trials (May 2011) gives a number of examples on how patient involvement improves the relevance and outcomes of clinical trials.

EPF also does not believe it should be mandatory to involve patients from the disease area that is being investigated, as it may not always be possible to find such a patient and this could potentially generate more administrative burden and an increase in the average delay for launching the trial. In such cases a patient organisation at national or European level could be invited to give feedback. An EU database of patient organisations, including organisations from different disease areas as well as national and EU wide platforms, would help researchers and national authorities in identifying suitable patient experts for involving in specific studies.

Capacity-building needs

Involving patients requires that they are given appropriate support and educational opportunities both about research and ethics generally as well as the specific area to be researched, to help their participation in scientific discussions. For example, the five-year initiative co-funded by the Innovative Medicines Initiative (IMI), European Patient Academy on Therapeutic Innovation6 will in the next years develop a number of resources to support patients' capacity.

However, those working with patients and involving them also need training. EPF calls for capacity building for bodies and individuals working with patients in clinical trials based on the recommendations of the projects VALUE+[7] and PatientPartner[8], to ensure that the benefits of this collaboration are fully realised. As an existing model of good practice, we refer to the European Medicines Agency, which since its establishment in 1995 has successfully included patient representatives in its scientific committees and scientific advisory groups.[9] EPF believes this model should be more widely disseminated among EU Institutions and national regulatory bodies as well as ethics committees.

EPF recommends:

8) The view of patients should be taken into account in assessing both parts I and II. Patient involvement should not be restricted by introducing qualifications but should be supported by appropriate capacity building and the involvement of patient organisations.
9) The Commission should develop guidelines on best practice for the implementation of patient involvement in different research and (multi)national contexts, drawing upon existing good practices and the experiences of the European Medicines Agency, Member States that already involve patients, EU-funded projects and patient organisations.
10) A European database of patient organisations including different disease areas and national and EU level platforms should be set up and maintained by the Commission.

[6] http://www.patientsacademy.eu/index.php/en/
[7] http://www.eu-patient.eu/Initatives-Policy/Projects/EPF-led-EU-Projects/ValuePlus/
[8] http://www.patientpartner-europe.eu/en/home
[9] "patient groups … provide a crucial patient perspective to the scientific discussions on medicines and have helped to provide valuable insights …. engaging with these stakeholders gives the Agency and the public more confidence and reassurance in its outcomes." European medicines agency: Fifth report on the interaction with patients' and consumers' organisations (2011) published in 19 September 2012. Available at http://www.emea.europa.eu/docs/en_GB/document_library/Report/2012/10/WC500133475.pdf

6. Ethics review

The Regulation makes no reference to ethics review. Instead, the wording of Article 9 reflects the previous Directive content pertaining to ethics committees and the Helsinki Declaration. However, EPF believes that to avoid uncertainty, the Regulation should state explicitly that ethical review is required. EPF does not accept that ethical aspects of clinical trials should be a matter for each Member State, to be assessed under part II of the assessment report. Scientific and ethical parts of the assessment cannot be artificially separated. The distinction between parts I and II is therefore artificial.

In EPF's view the current fragmentation in ethics reviews is a major problem that needs to be addressed by the Regulation. Fragmentation is caused by the existence of numerous ethics committees at different levels (national, regional, local)[10] and by divergence of procedures and values leading to divergent interpretations. This is neither ethical nor good for patients or science. The fundamental principles of medical ethics are universal, and patients everywhere in the EU should enjoy the same ethical standards.

The need for more patient involvement in ethics committees has been highlighted many times. Advances in medicine are possible only with the voluntary participation of patients, who make available their bodies for research. Patients not only have a moral right to have their views included in ethics assessment, but their involvement can improve the quality of the ethics review.[11] In order to respect the contract of trust between patient and researcher, the knowledge produced by research must be of high quality, and the outcomes must be robust. The design of the trial must be ethical from the patients' perspective. Nevertheless, the opinions of ethics committees do not always incorporate patients' views. In some EU Member States, patients are involved, but the majority of ethics committees do not include patients. Best practices and experiences of patient involvement in ethics review, both from Member States where this is already working, and from specific research projects such as U-BIOPRED[12], should be more widely shared.

EPF recommends:

11) In the interests of European patients and public health, the procedures and principles of ethical review should be better harmonised through sharing of good practices and guidelines developed at EU level. EPF recommends that the Commission sets up a multi-stakeholder platform, possibly modelled on the HTA collaboration network (EUnetHTA), to share best practices and develop guidelines/quality standards for ethics review across the Union. This platform should include all the relevant stakeholder groups, including patients.
12) The participation of patients should be embedded in all ethics review. Good practice in patient involvement should be identified, documented and shared, through the multi-stakeholder platform referred to above. Furthermore, EPF calls on Member States to make all efforts to ensure

[10] Impact Assessment Part 2, SWD(2012) 200 final, page 24.

[11] Please see extensive examples given in EPF's statement on the review of the EU clinical trials directive (13 May 2011), pages 3-8.

[12] Unbiased BIOmarkers in PREDiction of respiratory disease outcomes, a 5-year project (2008-2013) funded by IMI (EC FP7-EFPIA partnership) that deals with clinical trials; the Ethics Committee has four patients' representatives out of 11 total members. Patients' representatives are present at the Safety Monitoring Board and there is a Patients' Input Platform to give constant feedback into the project. Patients offered their help with the recruitment of the interested subjects too. The Commission has several times presented the project as a best practice with regard to patients' involvement.

that ethics committees in their territory include representatives of patients as well as lay persons in their functioning.

7. Information to patients

All patients and trial subjects should have access to the same quality of information provided about clinical trials, regardless of where in the EU they happen to live. What is perceived as high quality information does not differ for patients living in different countries.[13] Despite existing guidance, there are still unacceptable differences in the quantity and quality of information provided to patients in different Member States. EPF's members feel addressing the lack of, or inadequate quality of information around clinical trials is of paramount importance.

Patients' access to quality information is closely linked to their willingness to participate in clinical trials, as well as their commitment and adherence within trials.[14] A lack of information is apparent throughout the process: patients often do not know how to enrol in a clinical trial; they often do not know what they are participating in;[15] and they are not informed of the results or outcomes of the trial in which they participated.

Regrettably, this crucial issue is not addressed in the draft Regulation, which leaves the question of information entirely in the hands of Member States. EPF does not accept that information provided to patients should be of a different quality in different Member States. Member States may need to address specific aspects of information documents that are language or culture-bound, but the core elements of information and recommendations on the process of providing information, use of different tools, etc. should be agreed at EU level and implemented across the EU , and assessed in a coordinated way. The EU should moreover set the standard for trials conducted outside the EU also in this regard.

Many patient organisations have concrete experience of providing information to patients on clinical trials, often using innovative, user-friendly formats.[16] EPF has described several examples in our previous statements on clinical trials[17] and we believe they should be more widely shared and used. The involvement of patient organisations can also be very helpful in case of problems with the recruitment process.

EPF recommends:

13) The provisions under Article 29 (two) should refer to the core quality principles adopted by the High-Level Pharmaceutical Forum.[18]

[13] see for example the "core quality principles" on information to patients, developed by the High-Level Pharmaceutical Forum and endorsed by all Member States in 2008.

[14] Sood et al., "Patients' attitudes and preferences about participation and recruitment strategies in clinical trials". *Mayo Clin Proc* 2009;84(3):243-247; Eldh AC, Ekman I, Ehnfors M (2008). "Considering patient non-participation in health care". Health Expectations, 11, pp.263-271.

[15] For example Edwards SJL, Lilford RJ, Hewison J, "The ethics of randomised controlled trials from the perspectives of patients, the public, and healthcare professionals". BMJ 1998;317:1209–12;

[16] Elberse et al., "Patient involvement in agenda setting for respiratory research in the Netherlands", European respiratory Journal, vol.40 no.2, pp. 508-510.

[17] see EPF's website, www.eu-patient.eu

[18] According to these, information to patients must be objective and unbiased; reliable; evidence-based; up-to-date; transparent; patient-oriented; relevant; understandable; accessible and consistent with statutory information where

14) Core requirements for information quality should be assessed under part I of the procedure, while only genuinely national aspects would be assessed under part II. Patient involvement should be ensured at both levels.
15) The core elements of information to patients and guidance on implementation should be developed at EU level to ensure equally high quality throughout Member States. This should take place through a multi-stakeholder platform coordinated by the European Commission, and with the involvement of patient organisations.
16) Patients should be given information on the results of the clinical trial they have participated in, once it is finished. The results should be available in plain language.

8. Informed consent

Informed consent is a core prerequisite for enrolling any person in a clinical trial. Regrettably there are still large disparities in informed consent across the EU, both in terms of quality and quantity of the information provided, and the effectiveness of the process. Informed consent is still sometimes regarded as a ritual, rather than a crucial means by which patients are able to fully comprehend and evaluate the risks and potential benefits they will be taking in participating in a clinical trial.[19] Patients often do not recognise written consent as serving their interest, but rather the interest of researchers and hospitals.[20] A key problem with the informed consent is that it is seen primarily as a legal document. Nevertheless, in many cases the problems appear in the process rather than the documentation.[21]

EPF cannot accept that some patients in the EU – or outside – should have 'better' informed consent than others. We believe there must be core elements in an informed consent (documents and process) that are the same for all. Moreover, if there is no common standard, organisations could prefer trials in countries that are less strict in their requirements regarding informed consent and /or move their trials outside the EU. Therefore the conditions regarding patient information and informed consent should be made a basic requirement before the clinical trial may commence.

EPF recommends:

17) Informed consent should form part of the coordinated assessment under part I (core elements), as well as under part II (specifically national/language and culture-bound elements).
18) EPF calls for core requirements/elements to be developed at EU level, drawing upon existing best practice.[22] This should be done through a multi-stakeholder collaboration coordinated by the European Commission.
19) Article 29 should describe the conditions for informed consent more precisely, including specifying that information should be given orally and in writing prior to obtaining informed consent; adequate time should be given to consider the decision; informed consent could be revoked at

applicable. Core quality principles on information to patients endorsed by stakeholders and EU Member States (2008): http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/itp_quality_en.pdf

[19] Edwards J, Lilford R, Hewison J (1998). The ethics of randomised controlled trials from the perspectives of patients, the public and health care professionals. *British Medical Journal*, 317, pp. 1209-1212.

[20] Akkad A, et al. "Patients' perceptions of written consent: questionnaire study". British Medical Journal. 2006 Sep; 333 (7567):528.

[21] Project website: www.patientneeds.eu

[22] Such guidelines should draw on existing best practice, such as Alzheimer Europe's publication 'The ethics of dementia research' which gives recommendations on informed consent to dementia research.

any time; and attention should be given to the specific information needs of particular patient populations.

9. The low-intervention clinical trial

EPF welcomes the new category of low-intervention trials. This is particularly relevant to academic and other non-commercial trials, which often aim to compare existing treatments to find the best therapeutic strategy, rather than testing completely new treatments. The provision will make it easier for non-commercial sponsors to run such lower-risk trials without having to face high costs and complicated administrative requirements. The new category can thus help foster research that addresses some of patients' key priorities that are currently poorly addressed because they are not commercially attractive, including as comparing medical vs. non-medical strategies for chronic disease management.[23]

There is a potential concern that a sponsor may claim trials as low intervention to get the benefit of this status, while patients may judge otherwise. It is crucial that applications are diligently assessed, including a patient's perspective on the risks involved: balancing risks and potential benefits is a very disease specific, intervention specific, and therefore patient specific issue. EPF notes that the provision for patient involvement (Article 9) applies to assessment of whether a trial is low-intervention or not. This is absolutely key to arrive at an accurate assessment of the risk classification.

EPF recommends:

20) A patient perspective should be incorporated in the assessment of whether a trial is a low intervention one or not.

10. National indemnification mechanism

EPF welcomes the national indemnification mechanism. This proposal addresses a particularly important aspect that contributes to the high cost of running clinical trials.[24] Such costs pose a barrier to commercial but in particular academic and other non-commercial research. EPF strongly urges Member States to adopt this provision or an equivalent system to ensure a reasonable cost while guaranteeing that all patients are indemnified for damage that may occur in clinical trials.

EPF recommends:

21) Member States should implement the national indemnification mechanism to ensure that all patients are indemnified for damage when participating in clinical trials.

[23] See discussion in Evans I, Thornton H, Chalmers I and Glasziou P, *Testing Treatments*, 2nd edition p. 122-9. Available at http://www.testingtreatments.org/wp-content/uploads/2012/09/TT_2ndEd_English_17oct2011.pdf

[24] Commission estimates that across the EU, some EUR75 million are paid in insurance costs each year while the damages paid amount to less than EUR200,000.

C. Provisions on specific population groups

1. Minors and incapacitated people

EPF is broadly satisfied with the provisions concerning minors and incapacitated persons. We would stress that the views of people representing the target population should be sought whenever possible, as they can provide advice on personal ethical and practical questions regarding trials in such populations. Patient organisations can identify such individuals, or can be consulted as representatives of their members.

There may be rare occasions when people with such conditions are unable to voice their views (e.g. people with profound learning disabilities) when opinions from relatives and other carers may be appropriate. People concerned are best placed to decide on the need for 'protection' and weigh this up against the potential benefits of research. This is important because ethics committees and other regulatory bodies may err on the side of over-protection and impede scientific advances in these populations. To facilitate the participation of persons with diminished capacity in research trials and enable them to make an informed choice, it is important to have an "easy read" versions of the regulars documents available.

We also strongly agree with Article 30(f) that "such research relates directly to a life-threatening or debilitating medical condition from which the subject suffers". Importantly, we wish to point out that this section implies that research subjects who lack capacity can participate in trials for conditions other than that which causes their incapacity. For example, research subjects with a rare life-threatening cancer, but also dementia, should be allowed the opportunity to participate in a trial on the rare cancer so that they are treated equally with those who have capacity. We wish to uphold the principle of equity: people with dementia and other causes of mental incapacity should not be disadvantaged just because of their incapacity.

EPF recommends:

22) In designing and assessing trials involving minors or vulnerable groups, the views of representatives of the target population should be sought whenever possible.
23) In trials involving persons with diminished capacity, information and informed consent documents should always be made available in "easy read" versions to facilitate informed decision.
24) Persons with dementia or other form of incapacity should be supported as much as possible to take part in appropriate clinical trials. They should not be excluded from clinical trials purely based on the incapacity.

2. Clinical trials in emergency situations

In principle, EPF welcomes rules that will facilitate vital research. However, the protection of the subject must be maintained, and the well-being of the individual research subject must take precedence over all other interests.

The question of who takes a decision on the case of emergency to go ahead with the clinical trial varies between Member States. In principle, this decision should be made by an independent third party, but researchers have argued that obtaining such third-party consent often loses valuable time when the urgency of the situation does not allow for any time to be lost. EPF believes that this is very much

a question of case-by-case assessment. It is crucial therefore that such studies are carefully assessed by an ethics committee. Where possible, a panel consisting of representatives of the target patient population could be consulted to elicit their views as to whether in a hypothetical case scenario they would themselves wish to be part of a trial.

The Article does not define "minimal risk". US regulations define minimal risk as "Minimal risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons". We would suggest that this definition could be adapted to be relative to the life of the specific research subject rather than healthy persons in general.

EPF recommends:

25) Clinical trials in emergency situations should be particularly carefully assessed by an ethics committee involving patient representatives, particularly regarding the risk posed to the subject.
26) Where possible the views of representatives of the target population should be consulted.

D. Transparency and access to clinical trials data

1. The EU database

Article 78 sets up the EU database for clinical trials. This database "shall be publicly accessible unless … confidentiality is justified", which may be on the grounds of protecting personal data; protecting commercially confidential information; and ensuring effective supervision of the conduct of a trial by Member States (such as information about upcoming inspections).

EPF welcomes the principle of public access unless otherwise justified. In this context we believe it is necessary to define what constitutes "commercially sensitive data". We believe this definition should be as narrow as reasonable, in favour of maximum public transparency while still protecting legitimate commercial interests. An Access Policy should be developed and implemented for the database with the involvement of civil society, including patient organisations. The database should be as user-friendly as possible.

EPF recommends:

27) The EU database for clinical trials should be set up to be as user-friendly as possible. In consultation with all user groups, and an access policy should be developed and implemented.

2. Publication of trial results

Article 34 specifies that within one year from the end of the trial, the sponsor is obliged to submit a summary of the results to the EU database. The Article does not, however, specify what such a summary should contain. Furthermore, there is no obligation to give any reasons for terminating a trial early.

EPF has for a long time called for the publication of all results of all clinical trials in a timely manner, regardless of the outcomes.[25] Ensuring that after a research project finishes, the results are promptly published, can arguably be said to be as important as the approval of the trial in the first place. Any results, even of trials that "failed" or did not produce expected outcomes, adds to the totality of our evidence-base and can help target future research.

In EPF's view the provision in Article 34 should be more strongly and precisely framed. The summary is not sufficient. Therefore, the specific content of the results that should be published on the EU database should be defined in detail. EPF calls for clear standards regarding what information the database needs to contain. These standards should be developed with the involvement of civil society, including patient organisations and researchers, to ensure they address all groups' information needs. The results information should include a summary in lay language.

It is important also that the reasons for any early termination of a trial are published in the EU database. Reasons could include that the drug being tested did not appear to be effective, or had an effect other than intended, or that there were too many side effects – any of which could be vital information for patient safety as well as for future research in order to avoid duplication. There should be an obligation on the researchers and sponsors to notify the Member States of the reason for any early termination of a trial and that this should be made available on the public EU database.

EPF recommends:

28) All clinical trials should be registered prior to their start in the publicly accessible database. The start and end of recruitment should be published.
29) Reasons for early termination of a clinical trial should be published in the database.
30) All relevant updates to the information concerning a trial should be posted on the database, such as measures taken by Member States to terminate, suspend or modify a trial, as well as updated information on the benefit-risk balance or any urgent safety measures taken.
31) The results of all trials should be published on the database within one year in a format that includes all the relevant information, including a lay summary. The Commission should develop guidelines in consultation with stakeholders, including the research community and patient and consumers organisations, and to specify the exact content and format of the information that should be published.

3. Wider transparency of data from clinical trials

For patients and carers, the most important thing is usually access to results of clinical trials, with concrete and reliable information translating in simple language the conclusions emerging from the trial, rather than trial data as such. However, a number of stakeholders are calling currently for the publication of all the raw (patient-level) data from each clinical trial.

EPF is in principle in favour of the principle of sharing clinical trials data, so that other researchers can revisit and reanalyse the data. This is in the interest of good science and in the interest of the public. It can often be in the interest of patient associations, also. The making available of patient-level data

[25] see for example EPF's position statement from January 2010, http://www.eu-patient.eu/Documents/Policy/ClinicalTrials/EPFs_Response_to_Clinical_TrialsConsultation.PDF

in the public domain for anyone to access goes beyond the question of making available such data for legitimate research purposes.

EPF does not believe that the proposed Regulation offers an appropriate instrument to address this issue. We suggest that it needs thorough discussion and reflection involving all stakeholders and the wider public. All the implications and potential – intended and unintended – consequences of data sharing need to be carefully considered, including questions related to the timing of data sharing; what level of data is made available, i.e. raw, processed, aggregate data sets, etc.; the security of the data that is shared and the protection of trial subjects' personal data; and the potential implications for patients' willingness to participate in trials were patient-level data were to be made available to other researchers or even in the public domain.

EPF therefore welcomes the recent efforts of the European Medicines Agency to open discussion on how to publish data from clinical trials.[26] We are committed to participating in this public debates in order to find a good solution that serves both science, patients and the public interest. EPF will undertake further work with its membership on this issue.

E. Other provisions

1. Clinical Trials Coordination and Advisory Group

Article 81 establishes a Clinical Trials Coordination and Advisory Group (CTAG), composed of national contact points. This group should be based on the principles of good governance, including transparency, and include a sufficient number of representatives of relevant stakeholder groups, health professionals and patient organisations, in its functioning.

EPF recommends:

32) The CTAG should ensure the involvement of adequate numbers of representatives of relevant stakeholder groups, including patients.

2. Clinical trials taking place outside EU

Clinical trials taking place outside the EU should apply the same standards of safety and protection of patients as in the EU, including that the safety and well-being of participants must prevail over all other interests. The wording of Article 25 is not strong enough in our view.

EPF emphasises the importance of the following aspects[27]:

- Free, informed consent, particularly regarding patients in potentially vulnerable situations (such as women in male-dominated societies) and children. It is crucial to ensure that the

[26] http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/11/news_detail_001662.jsp&mid=WC0b01ac058004d5c1

[27] Based on EPF's input to the European Medicines Agency's "Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities", which came into effect in May 2012. The paper is available at http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500125437.pdf

informed consent procedure is meaningful and robust and ensures the protection of the clinical trial participants/patients.

- Information provided to patients/trial participants must be adequate, comprehensive and understandable, and respect the principles of the Declaration of Helsinki as well as the International Ethical Guidelines for Biomedical Research involving Human Subjects by the Council for International Organisations of Medical Sciences in collaboration with the WHO28.
- Free (or affordable in the local context) treatment after the trial ends should be ensured for trial participants, and for the wider community as appropriate (see below). Arrangements regarding this should be described in the protocol.
- EPF is supportive of the language of the declaration of Helsinki (2008) that research "involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research."
- Appropriate and effective sanctions to address cases where non-compliance does occur.
- Patient representatives should be involved in clinical trials.
- EPF is also strongly supportive of capacity building efforts to support countries where the regulatory framework is weak. This should include sharing examples of good practices of civil society and patient involvement; protection of groups that may be in situations of vulnerability; and good practice and how to ensure equitable access to treatment following the end of trials.

EPF recommends:

33) Article 25 should clearly state that clinical trials conducted outside the European Union must comply with the provisions of the Regulation, and the Declaration of Helsinki, rather than principles equivalent to those.

3. Access to treatment post-trial

EPF has long advocated for free availability of the treatment being tested – assuming the investigational product is authorised and turns out to be the most beneficial one for the patient – after the end of a trial. Ensuring appropriate access to post-trial treatment is not only an ethical issue, it is also beneficial to sponsors and researchers, as it can be a major motivation for patients willingness to volunteer for trials, and thus can help sustain a high level of patient participation. But despite patients reporting that they would like this to be part of the protocol, it is not always the case.

Annex I of the Regulation specifies that the trial protocol must include "a description of the arrangements for taking care of the subjects after their participation in the trial has ended, where such additional care is necessary because of the subjects' participation in the trial and where it differs from that normally expected for the medical condition in question." This is appropriate, but it is not enough.

A minimum requirement should be to provide full and open information to all potential trial participants on whether 'post-trial' treatment will be available, and whether they would be expected to pay for it. However, we would also suggest that there is a moral obligation on researchers and

[28] www.cioms.ch/.../layout_guide2002.pdf

sponsors to secure free or affordable post-trial treatment to all trial participants, provided that the drug is authorised. Paragraph 33 of the declaration of Helsinki (2008) states: "at the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care benefits."[29]

EPF recommends:

34) National competent authorities and trial sponsors should be required to consider options for securing free, or affordable in the local context, post-trial treatment to all trial participants and the wider community where appropriate, before research is even started.
35) Sponsors should be required to describe in the trial protocol and in the clinical study report the provisions made with respect to access to treatment post trial, provided that the drug is eventually authorised.

F. Requirements for the application dossier (Annex)

EPF welcomes the annexation of the requirements for the trial application dossier to the Regulation itself. We feel this adds clarity to the process. However, the requirements need to be further specified and strengthened.

EPF calls for the following requirements to be included in the application dossier:

Evidence base

The protocol should, when discussing the relevance of the clinical trial, reference all existing research data, including systematic review and meta-analysis to ensure there is justification for further research and that all the relevant facts about the IMP are known. The protocol should include a description of how the evidence was obtained, selected and assessed, and what the study adds to the totality of evidence when added to previous work.[30] Failure to review thoroughly and objectively all the existing evidence by high quality systematic reviews and meta-analysis can result in trials being done on the basis of incomplete data, where patients can be harmed – either by giving them potentially dangerous substances or by depriving a comparison group of a substance that has already proven beneficial. Such research is redundant – studying things that are already known – which is fundamentally unethical, and also a waste of precious resources.

Patient involvement in priority setting

Research questions that address issues that patients consider important should be prioritised. When it comes to a discussion of relevance, the protocol should mention whether there was patient involvement in identifying the research topic/questions and if so, description of that involvement. Research applications where there is meaningful patient involvement in defining the research questions and protocol, should be given priority in all EU calls for proposals.

[29] From the patients' perspective, access implies both availability (on the market) and affordability (in the local context) for the individual patient.

[30] Adapted from the requirements of *The Lancet* for submitting research articles: (Clark S, Horton R. Putting research in context – revisited. *Lancet* 2010;376:10-11 cited in *Testing Treatments* (2012), p. 103)

Ethical considerations

The protocol should include a statement on how ethical considerations have been addressed and how the principles of the declaration of Helsinki have been adhered to.

Gender and age balance

EPF believes that appropriate age and gender balance in clinical trials is of critical importance. If the trial subjects do not reflect a balanced distribution in age and/or gender, this should be justified and explained. EPF wishes to stress that an underlying principle of biomedical research is that participants/patients entering clinical trials should be reasonably representative of the population that will be later treated by the medicinal product, as laid down by the ICH Guidelines. Sex and gender differences exist in the incidence, treatment responses and prognosis of a range of diseases. In addition, gender and age may influence the effects of medication. Therefore, only a fair gender and age balance will allow for a robust evidence-based benefit/risk assessment for all patients male and female. [31]

Post-trial access to treatment

In line with the Declaration of Helsinki, the protocol should describe the provisions for making the treatment available to trial subjects after the end of the trial, provided that man the investigational treatment is approved for marketing.

Compensation for harm

In line with the Declaration of Helsinki, the protocol should contain information about the provisions for treating and/or compensating trial subjects who are harmed as a consequence of participation in the trial.

Conflicts of interest and financial relations

In line with the Declaration of Helsinki, the protocol should contain information regarding funding, sponsors, institutional affiliations and any other potential conflicts of interest, and how these are addressed.

[31] for more information on gender and clinical trials, see the position paper of the European Institute for women's health, available at http://eurohealth.ie/2013/01/14/eu-commission-proposal-for-clinical-trials-regulation/