

EPF's RESPONSE TO THE COMMISSION PUBLIC CONSULTATION ON THE CLINICAL TRIALS DIRECTIVE 2001/20/EC

19 January 2009

Introduction

The European Patients' Forum (EPF) welcomes the Commission's initiative to consult the public on the assessment of the functioning of the "Clinical Trials Directive" 2001/20/EC and is pleased to send its contribution. We see this as a key opportunity to review the legislation in ways that should produce a better, more proportionate and patient-centred approach to trial design and regulation, and the possibility for reforms that involve patients through the entire research process from the "idea" phase to proven intervention.

Fundamental importance for patients

The effectiveness of clinical trials throughout the EU is of fundamental importance for EPF and its members. Clinical trials influence, ultimately, patients' access to new and improved medicines and treatments, and are a major mechanism for identifying and responding to unmet medical health needs.

A good regulatory framework is one that incorporates and balances all relevant stakeholder inputs and expectations, holding these in a creative tension while not being overly rigid or stifling novel, innovative approaches or techniques.

Patients have an obvious and central role and responsibility within clinical trials; they are the reason for their existence, they are the ultimate recipients of their successes, and most importantly for this consultation, it is they that provide the information and manage the personal risks that clinical trials necessitate.

Methodology around the consultation with EPF membership

A Memorandum to the EPF's membership was formulated to prepare EPF's response to the Commission's consultation on the Clinical Trials Directive. This was circulated to all EPF members with a request for input. A draft response was then developed and circulated before Christmas for EPF's members' comments. We also included input from other health NGO allies.

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In this response, we have drawn on evidence from the Value + project, the PatientPartner project which is coordinated by VSOP in the Netherlands, the INVOLVE group in UK, the RESPECT project on the meaningful involvement of young patients in clinical trials and the work we are undertaking with EMEA in relation to Third Country Clinical Trials and the Patients and Consumers' Working Party.

This response highlights a broad vision for genuinely patient-centred clinical trials and flags a number of core issues of relevance to all patients. Some of EPF's members will be also be submitting their own responses, from the perspective of their particular disease or interest area, and referencing their own experiences with the operation and impact of the Clinical Trials Directive as it currently operates within individual Member States, or across the EU.

EPF's response to the consultation

The Commission's consultation document is structured according to the specific themes and articles of the Clinical Trials Directive. The questions that are posed at the end of these themes tend to be highly technical and are not directly related to patients or patients' concerns. Therefore EPF's response does not cover the whole consultation document, but focuses upon an overarching vision for clinical trials in EU, to ensure that are genuinely patient-centred, and highlights the themes which are most important and relevant for patients.

The model of the clinical trial underpinning the current legislation in general terms is that of a multi-centre large scale study. Whilst this model may be appropriate when considering the development of small molecules for common diseases, it is increasingly inappropriate when the impact of new knowledge in genetics and biotechnology and the increasing importance of lessons learned from rare disorders are taken into account. The value of patient input to trials and other forms of biomedical research has been well documented by INVOLVE project¹ and PatientPartner project².

EPF would particularly like to focus on the inclusion of key patient issues that do not feature in the consultation paper, namely:

- Ensuring that there is meaningful patient involvement across all aspects of clinical trials, so that they are focussed on patients. We believe that this will enhance and improve the outcome of clinical trials. This may also increase patients' participation rates in clinical trials.

¹INVOLVE - Promoting public involvement in NHS, public health and social care research, <http://www.invo.org.uk/index.asp>

² PatientPartner Project <http://patientpartner-europe.eu/>

- Giving patients access to quality information regarding clinical trials
- Transparency concerning the results of clinical trials (even if the clinical trials failed or did not achieve the expected results).
- Meaningful informed consent, especially regarding patients from the mental health arena.

EU funded research (e.g. ICREL project³, PatientPartner project) has also demonstrated or is demonstrating the need for these areas to be addressed. We believe that the best way to address this need would be by the use of a “check list” or framework for those proposing to design and carry out a clinical trial. Such a list could include the following questions also to be put to different stakeholders – patients, regulators, doctors, etc. Their responses could then be compared, which would identify where there are agreements and where there is divergence. This would allow a more inclusive and creative approach to develop in the design and undertaking of clinical trials.

We would propose that any checklist contain and address the following questions (non-exhaustive):

1. What is the problem?
2. How does it relate to the overall picture/impact of the disease?
3. Why is this important?
4. What you propose to do about it?
5. Why do you think I can help you?
6. How long will it last and how much time will it take?
7. What do you think it will tell you that will lead to better prospects for patients with “x”?
8. What risks might be created?
9. How will you manage these?
10. What alternatives exist?
11. How good are they? etc

KEY ISSUE N°1 – MULTIPLE AND DIVERGENT ASSESSMENTS OF CLINICAL TRIALS

3.2 Weaknesses

The increased costs (2.5) and bureaucracy lead to a delay in new/ improved medicines reaching patients who need them. A part of the increased bureaucracy is created by the complex authorisation and assessment procedures (2.4 & 3.1), especially when clinical trials cover more than one Member State which happens in a significant number of cases.

³ICREL Project – European Forum for Good Clinical Practice <http://www.efgcp.be/icrel/>

Consultation item n°3: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

The declining numbers of patients participating in clinical trials in EU is of high concern: (50% less from 2007 to 2009⁴). For independent non-profit medical research, the increasing burden involved in planning and executing a clinical trial is a particular threat. While industry-driven research is important, desirable, and rather well-regulated under current legislation, academic research is also crucial for the provision of new knowledge, especially in fields that do not attract commercial interest, for instance because the number of patients is too small to make a viable business proposition out of a proposed clinical trial, or where industry has a conflict of interest.

It is also therefore important to provide a framework in the regulations for “non-commercial” trials. The US investment in head to head comparisons provides an example of where the EU could do more work.

Bringing established compounds in new applications, or developing off-patent products for new groups of patients are areas of activity that are more often than not initiated by academics, and then picked up by niche SMEs.

Surgical trials, the development of diagnostics linked to therapeutics are also in need of appropriate, risk/benefit based regulation.

This is of extreme importance for patients with rare diseases, who often do not cover a significant number of the population, to be given consideration for clinical trials. In order to still enhance scientific developments in these areas restrictions on academic research needs to be re-evaluated.

A recent INVOLVE study⁵ has explored the impact of patient and public involvement through an in-depth review of published literature, drawing together a wealth of examples. It shows that patients and the public always offer unique, invaluable insights. Their advice when designing, implementing and evaluating research invariably makes studies more effective, more credible and often more cost efficient as well.

INVOLVE research has generally highlighted that patients' involvement in academic research makes it better targeted for people who need it. Patients can play an important role by helping to ensure that the issues that are identified and prioritised are important to them.

⁴ Table 3: Number of planned clinical trials participants in EU, European Commission's consultation paper: “Assessment of the functioning of the clinical trials Directive” 2001/20/EC

⁵ *Exploring Impact: Public involvement in NHS, public health and social care research*, November 2009, http://www.invo.org.uk/pdfs/Involve_Exploring_Impactfinal28.10.09.pdf

KEY ISSUE N°1 – MULTIPLE AND DIVERGENT ASSESSMENTS OF CLINICAL TRIALS

3.2 Options to address the issue as regards the assessment by Ethics Committee

Although ethical issues fall within the remit of Member States, it is worthwhile considering how cooperation and exchange amongst national Ethics Committees could be promoted in order to improve the ethical review of clinical trials.

Three possible options are proposed:

- 1. One-stop shop for submission of a request for authorisation of a clinical trial to the National Competent Authority and the Ethics Committee – (advantage: reduce the administrative burden of multiple submission of information to separate actors)*
- 2. Strengthening networks of national Ethics Committees involved in multinational clinical trials – (advantage: stronger cooperation of Ethics Committee to exchange views and experiences)*
- 3. Clarifying the respective scope of assessment of National Competent Authorities (NCA) and Ethics Committee – (advantage : clearer identification of their respective roles and responsibilities)*

As a starting point, EPF endorses the three main ethical principles for the purpose of research, that are outlined in the reference literature⁶ in the field: respect for persons, beneficence (defined as the ethical obligation to do good and avoid harm) and justice (defined as a fair distribution of burden and benefits of research).

We would also argue that the safety and wellbeing of the patients involved in clinical trials should be of paramount importance, and when in conflict, it should prevail over the interests of science and society.

Furthermore, the need for more patients' involvement as part of ethics committees was several times highlighted. Ethics Committees should include, for example, alongside scientists and health professionals, patients organisations' representatives as well as lay persons qualified to represent the cultural and moral values of the community and to ensure that the rights of the patients participating in the clinical trials are respected. However, a clear distinction between patients and lay persons should be made, and in some countries (for example in the Netherlands), it is

⁶ The Charter of Fundamental Rights of the European Union (2000),
The Council of Europe's Convention on Human Rights and Biomedicine (1997) and its Additional Protocol on Biomedical Research (2005),
The Universal Declaration of Human Rights of 1948,
The United Nations' Convention on the Rights of the Child (1989),
The Universal Declaration on Bioethics and Human Rights (UNESCO, 2005),
The Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997),
The International Declaration on Human Genetic Data (UNESCO, 2003),
The CIOMS-WHO International Ethical Guidelines for Biomedical Research Involving Human Subjects (Geneva 2002),
The Declaration of Helsinki of the World Medical Association (2008) and the EU Ethical considerations for clinical trials on medicinal products conducted with the paediatric population (2008).
The ICH E6 guideline on Good Clinical Practice (1995)

forbidden by law that patients fill in the position of the lay persons. The lay persons – usually ethicists or lawyers - have often no contacts with patient groups and are not able to reflect on developments, from a patient perspective.

Given the high number of ethics committee across EU and the fact that research is more centralised and globalised, EPF suggests to concentrate on option 1 and option 2, to make research more workable and to achieve better results.

For example, in The Netherlands, 16 of the 30 ethics committees looked at a protocol for a study on the use of probiotics. At the end of the study, it became clear that much went wrong with this study. But nevertheless, none of the 16 ethics committees saw the shortcomings of the study proposal (*source EGAN – European Genetic Group Alliance*).

A recent survey on lay and patients' representatives of ethical committees in the UK showed that the majority of the surveyed participants felt that their views as a patient member were fully taken into account in the deliberations of the ethical review committee⁷.

Regarding the three options proposed in the consultation document, EPF considers that they are not mutually exclusive. EPF would strongly encourage further cooperation among ethics committees in order to exchange experiences at operational level about the assessment of the requests received for authorisation of clinical trials and the clinical trials processes.

KEY ISSUE N°3 : REGULATORY FRAMEWORK NOT ALWAYS ADAPTED TO THE PRACTICAL REQUIREMENTS

Consultation item n°9: Can you give examples for an insufficient risk-differentiation? How should this be addressed?

Patients (due to their individual experience and specific situations) will perceive the risk undertaken by a clinical trial differently. As the current Directive uses a 'one-size-fits-all' approach regarding risks of clinical trials this may jeopardise the safety of the patient, and/ or constrain or undermine the impact of the clinical trial.

Research⁸ shows that patients seem to often overestimate the benefits of the treatments of the clinical trials. Unrealistic expectations and false hopes need to be addressed already at the early stage of the clinical trial process and should ideally be dealt with in the informed consent phase. However, there are still significant differences in informed consent across EU both in term of quality and quantity of the information provided. The narrow relationship between informed consent and risk/benefit differentiation is proven by the example below.

⁷ INVOLVE Project, *Survey of lay/patient members of research Committees*, 2009

⁸ Cheng, J. et al. (2000). Impact of Quality of Life on Patient Expectations. Regarding Phase I Clinical Trials. *Journal of Clinical Oncology*. Vol 18 (2). pp 421-428.

In an ongoing trial on an already approved medicine patients with thalassaemia were switched from a combination therapy to the newer medicine in a way which many patient leaders considered inappropriate, given their medical condition, and thus unethical. They raised the issue expressing their serious concern. The patients' organisations' office then wrote to some of the scientific experts involved in these trials, and their response was unequivocal: they had no ethical concerns whatsoever since the patients were "under close medical supervision and had signed the consent forms". They were thus considered "fully informed". (source Thalassaemia International)

On the other hand, patients who have an extremely serious life threatening disease will very often have a different perception of risk linked to a clinical trial for innovative treatment where this might be the only and or last chance of survival. They will analyse the risks & benefits differently, and will be more willing to take high risks for lesser benefits, or a lesser guarantee of benefit.

Other studies⁹ revealed that there is a sense that informed consent is still regarded as a sort of ritual and not as a means by which patients are able to fully comprehend and assess the risks they will be taking in participating in a clinical trial.

This has raised the issue of how meaningful the concept of informed consent actually is, and how can we ensure that it is indeed fit for purpose and increases the safety and confidence of patients (patients are able to fully engage in a discussion about the risks and benefits through their participation).

On this important issue EPF would therefore propose the following improvements regarding the risk / benefit differentiation:

- Specifically link the risk / benefit evaluation with the informed consent phase of the clinical trial.
- Stimulate and facilitate contacts between clinical research and patient organisations.
- Coherent and comprehensive information to patients about clinical trials is needed. This information needs to be in an appropriate language and format and understandable for the patient or his / her representative.
- Patients' representatives should be involved at a governance level: in the setting of research priorities, protocol development and ethical review.

KEY ISSUE N°5 : ENSURING COMPLIANCE WITH GOOD CLINICAL PRACTICES IN CLINICAL TRIALS PERFORMED IN THIRD COUNTRIES

⁹ 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.

Consultation item n°16: Please comment. Do you have any additional information, etc?

EPF is cooperating on this matter with the International Alliance of Patients Organisations (IAPO), which has an extensive experience in this area. EPF also participated in 2009 in the work of the EMEA's Working Group on Third Country Clinical Trials and contributed to the reflection paper elaborated by this group.

Firstly, EPF calls for a meaningful involvement of patients' organisations and patients' representatives in clinical trial process performed in countries outside EU. Patients can be involved in protocol reviews and can give advice on regulatory issues surrounding clinical trials.

Concerning vulnerable patients' groups who participate in clinical trials outside EU, specific measures and means of protecting their rights and wellbeing should be strictly applied.

Research should be undertaken only if its results have the potential to produce real and direct benefit to the patients' health. Clinical trials are meant as research studies and should not be communicated as a treatment option. However, in reality, taking part in a clinical trial is for many patients the only treatment option. In most cases, a direct benefit to the patient's health cannot be established. If this were a prerequisite to performing clinical research, then none would get done.

A key concern is that in many developing countries, patients with low economic status participate in clinical trials primarily because they have very limited access to healthcare, and participating in a trial may offer them a access to better medical care and treatment. Those undertaking clinical trials have an ethical responsibility to ensure that trials due not suffer a loss of health status after a trial has been completed, and where possible, that effective treatment or healthcare is provided to them after the research is over.

EPF would encourage those hosting clinical trials regularly in third countries to invest in better healthcare programmes, and to ensure that the benefits of any successful trials are made available equally in those countries.

Finally, specific procedures to guarantee the respect of different cultures and traditions of the population involved in research should be given due and fully consideration in the development and implementation of clinical trials undertaken in third-countries.

Consultation item n°18: What other aspect would you like to highlight in view of ensuring the better regulation principles? Do you have additional comments?

As highlighted in the introduction, some of the core concerns of patients are not covered by the questions posed in the Commission's consultation document. Although the Directive attempted to improve the situation of patients in relation to clinical trials, there remain several gaps that should be addressed in any review.

These include:

1. Meaningful patients' involvement in clinical trials processes.

Patients are not only a research "subject" but should be actively involved in the clinical trials process. The Value+ Project¹⁰ indicates the definition of meaningful patient involvement and the benefits this provides for projects, activities and research. The project findings highlight that patients' involvement in clinical trials improves several critical aspects of clinical trials research. Among these there are:

- Patients' perspective on ethical and risk / benefit dilemmas;
- Managing expectations;
- Better adherence which improves costs effectiveness;
- Patient and public confidence in clinical research which stimulates involvement in participation of clinical trials research.

A survey undertaken by the PatientPartner Project¹¹ (which consisted of 205 patients organisations from 31 European countries) highlighted that there are a number of roles that patients' organisations can play regarding clinical trials research:

- provide information and explanations regarding clinical trials for patients' communities they know well;
- give advice on ethical and regulatory aspects,
- review clinical trial research protocols or a clinical trial refunding request, and stimulate trust and participation of clinical trials.

The European Genetic Alliances' Network (EGAN) has developed a booklet¹² for patients with chronic diseases which brings together some of the questions that are frequently asked by those thinking about joining a clinical trial. It aims to provide clear information in a straight forward way so that patients and their families can make

¹⁰ Value+ Project. Meaningful Patient Involvement. (2009). *Value+ Handbook*. http://www.eu-patient.eu/projects/valueplus/resources/attached_documents/doc_epf_handbook.pdf and Consumers under the Public Health Programme 2008-2013

¹¹ PatientPartner Project. (2009). Identifying the Needs of Patients' Partnering in Clinical Research. *Survey Patients' Organisation on Level of Involvement*. <http://www.patientpartner-europe.eu/en/inventory/survey-patient-organisations/results/levels-of-involvement>

¹² EGAN - *FAQ on Clinical Trials*, <http://www.biomedinvo4all.com/en/research-themes/clinical-trials/>

informed decisions about taking part in a clinical trial if the opportunity arises. This is an illustration on how patient organisations can inform and educate their members.

Europa Donna has experience serving on trial committee, with for example members who serve on the Steering Committee, the Legal/ethics Committee and the Spreading of Excellence Committee of the Transbig/MINDACT trial which is supported by the European Commission.

The International Diabetes Federation – Europe highlighted strongly the importance of a patient/ client Council linked to every academic hospital/ health care institution to provide ongoing insight and expertise from a patient's rights, and also patients' responsibilities perspective. These are the norm in some countries, such as the Netherlands – but in many countries do not exist. Such Councils could play a fundamental role in nurturing a positive patient-centred environment for Clinical Trials to take place.

Finally, the National Voices' report "Access to Clinical Trials: Report of the deliberative event hosted by National Voices for the MHRA"¹³ recommends that there should be increased involvement for patients and patient organisations in the development, running and reporting of clinical trials. The report shows that this may lead to an increase in the participation rates for trials, and allow a greater degree of risk to be included in trial protocols.

2. Access to quality information at all stages of clinical trials

Research indicates that patients are often not provided with sufficient and comprehensive information regarding the clinical trial.¹⁴ This issue is closely connected with the informed consent phase of a clinical trial and the understanding of the risks involved by participating in that clinical trial. Moreover, the lack of information for patients regarding clinical trials is apparent across all stages of the process: for example, patients often do not know how to enrol in a clinical trial; they often do not know what they were participating in; they are not informed of the results or outcomes of the clinical trial in which they have participated.

3. Informed consent in an accessible language

All the international instruments on ethical and legal standards in medicine and in biomedical research endorse the requirement of informed consent.

¹³ National Voices - *Access to Clinical Trials: Report of the deliberative event hosted by National Voices for the MHRA*, November 2009, <http://www.mhra.gov.uk/Howweregulate/Medicines/MISGNewTechnologiesAdvisoryPanel/Earlieraccestonewmedicinesintheuk/index.htm>

¹⁴ 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.

As outlined above, informed consent – in a language which is accessible and understandable for the patient and his/her representatives - should be regarded as a meaningful pre-condition for the start of any clinical trial.

Before being asked to consent to participate in a clinical trial, a patient should be specifically given the information in an understandable form. This information should be recorded. It should cover information about:

- the nature, extent and duration of the procedures involved,
- available preventive, diagnostic and therapeutic procedures;
- arrangements for responding to adverse events;
- arrangements to ensure respect for private life and ensure the confidentiality of personal data;
- arrangements for access to information relevant to the patient arising from the research and to its overall results;
- arrangements for fair compensation in the case of damage;
- any foreseen potential further uses, including commercial uses, of the research results, data or biological materials;
- the source of funding of the research project/clinical trial.

All documentation (information and consent/assent) must be written in a lay-friendly language, wording appropriate to age, psychological and intellectual maturity of patients participating in clinical trials.

4. Clinical trials for paediatric patients

EPF argues that all paediatric clinical trials should ensure that procedures meet with legislation and current thinking on children's rights. In this regard, it would be helpful to consult children's rights organisations and collect their views on this matter.

The initial findings of the EU supported project RESPECT¹⁵ suggest that children and parents decide to participate in trials for reasons that span from personal benefit to altruism. There is however no re-assessment of their initial expectations, and the concrete reality of the trial is often different from what they had initially thought. There are clearly issues around autonomous and objective decision-making and around consent and assent: the children rely on the parents who in turn rely on the doctors. A neutral figure in support of children and parents, who could support their empowerment, has been envisaged. Patient organisations, for example, could fill this role. The findings of the interviews and focus groups also indicated that patients organisations should be actively involved in the setting of the trials as well as in ethics committees.

Finally the research indicated that the main focus related to clinical trials is on the protocol approval and the consent process. There is less attention on monitoring how

¹⁵ Relating Expectations and Needs to the Participation and Empowerment of Children in Clinical Trials <http://www.patientneeds.eu/>

the protocol is applied, how the consent is obtained and how children and parents live this experience. These aspects need to be better addressed in order to empower participants and conduct patient-centred trials.

5. Transparency regarding clinical trials across EU including learning from those clinical trials that have failed

At micro level, patients often have little access to the results of the clinical trial. Data¹⁶ also shows that this decreases the willingness of patients to participate in a follow up or second clinical trial. At macro level, even trials that have failed can reveal significant information for patient groups, particularly in certain disease areas.

A recent report¹⁷ from the national patients' organisation in UK (National Voices) highlights that there should be greater transparency in the way trials are selected, managed and reported, especially in regards to data about treatment failures and side-effects.

In order to increase transparency regarding clinical trials more user friendly databases should be created, that also include the results of and evidence from clinical trials. EPF believes that the establishment and widespread use of such databases would be a major step in encouraging more patients to become actively involved in clinical trials.

From this perspective, EPF welcomes the positive developments linked to the EMEA database of clinical trials (EudraCT) that will be publicly accessible in 2010. Protocol-related information of a large majority of clinical trials will be accessible to the general public who will be able to search for and to retrieve information on clinical trials registered in the EU/EEA. EPF will participate in a test session the mock up of the new external public web on the 4th of February.

6. Access to the treatment following the clinical trial

A key issue for patients is the free availability of the medicine/ treatment being tested following the completion or ending of a trial. It is not always the case that this is made available, despite our findings that many patients report that they would like this to be part of the protocol.

¹⁶ Sood, A., Prasad, K. & Wahner, L. (2009). Patients' Attitudes and Preferences about Participation and Recruitment Strategies in Clinical Trials. *Mayo Clin Proc.* 84(3) pp.243-247.

¹⁷ *Access to Clinical Trials: Report of the deliberative event hosted by National Voices for the MHRA*, November 2009, <http://www.mhra.gov.uk/Howweregulate/Medicines/MISGNewTechnologiesAdvisoryPanel/Earlieraccesstonewmedicinesintheuk/index.htm>

CONCLUSIONS

There is a demand for patients with serious diseases and conditions to participate in relevant, high quality research – and well designed clinical trials are an essential component of this. A revision of the Clinical Trials Directive provides a golden opportunity to create a regulatory framework that is conducive to such research.

The European Patients' Forum is committed to work closely with the European Commission and other relevant stakeholders in translating the vision and the core issues outlined in this response into more effective, patient-centred EU legislation on clinical trials.

The **European Patients' Forum** (EPF) was founded in 2003 to become the collective patients' voice at EU level, manifesting the solidarity, power and unity of the EU patients' movement. EPF currently represents 41 member organisations - which are chronic disease specific patient organisations working at European level, and national coalitions of patients organizations. EPF therefore reflects the voice of an estimated 150 million patients affected by various diseases in the European Union.

EPF's vision for the future is high quality, patient-centred, equitable healthcare throughout the European Union.