Briefing on transparency amendments to the Clinical Trials Regulation

A briefing to trilogue participants from AllTrials campaign and its European signatory organisations

November 2013

Briefing Aim:

This briefing has been prepared and distributed with the purpose of informing participants in the November-December trilogue discussions 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 (COM(2012)0369 – C7-0194/2012 – 2012/0192(COD)).

It is especially concerned with the issue of transparency in relation to clinical trial result reporting and therefore encourages the agreed adoption of amendments 30 and 250; amendments 193 and 253; amendment 191; amendments 29 and 152; amendment 35; amendment 194; amendments 247 and 248; and amendment 290 of the 10th June 2013 European Parliament ENVI Committee report.

Increased transparency in the reporting of clinical trial results is a public interest imperative

Around half of all clinical trials have not been registered properly and thousands of clinical trials have been conducted without the results ever being published. What was found in these trials is not available to regulators, doctors pharmacists and patients and could be lost forever leading to bad treatment decisions, missed opportunities for good medicines and trials being needlessly repeated. Millions of patients and their families have volunteered their time and put themselves at risk to participate in clinical trials on the understanding that, even if their participation does not benefit them personally, the findings generated will add to the body of medical knowledge and will benefit society and future patients. It is a betrayal of their trust that the findings from thousand of trials are kept behind closed doors. All clinical trials should be registered and a summary of the results reported.

Increased access to clinical trial information will have a number of benefits:

- **Enhanced scientific knowledge** Scientific research is self correcting. Research advances through critical analysis and review, which are essential for identifying flaws in study design, statistical errors, missed observations of both benefits and risks and the best ways to conduct further research. This process has been necessarily partial because of partial publication. Full publication will restore this vital part of the research checking process, which is the basis of greater confidence in research findings whatever their provenance. Even, especially, trials that produced negative results (that is, those where the intervention being tested did not result in a benefit for patents) add to the totality of scientific knowledge.

- **Improved decision making on treatments and medicines** and therefore better patient outcomes. With full information about effects and side effects, a better risk/benefit calculation can be made by doctors, and individual patients. Healthcare commissioners and regulators can make a more accurate cost/benefit assessment which ensures that the treatments available are those that are truly the most effective.

- **A richer research base for both industry and academia.** This means greater potential for collaboration and interdisciplinary work, more productive research, and potential value from unused Intellectual Property. The Head of the EMA recently wrote that, “we predict that it will help to increase the efficiency of drug development, improve cost-effectiveness, improve comparative-effectiveness analysis, and reduce duplication of effort among trial sponsors.”

- **Fulfillment of basic ethical standards:** The Helsinki Declaration says that all researchers who conduct research using human subjects have an obligation to publish what was found in that research. Conducting clinical trials on patients to discover something that has already been discovered, however unintentionally on the part of those conducting the research, is misleading participants, wasting resources on expensive and unnecessary research and putting patients at unnecessary risk1.

For years, patients who had suffered a heart attack were prescribed drugs to prevent heart rhythm abnormalities. By 1990, it was estimated they were killing between 40,000 and 70,000 per year. Had a trial conducted in 1980 suggesting the drugs were lethal been published, this catastrophe might have been prevented2.

- **Avoid unnecessary clinical trials:** More reporting of clinical trial results will mean that future research can be targeted better. Commercial research organisations have told us that they have been contracted to run trials they know have already been conducted, but because the trials were not registered or results reported, this information was not public, with a financial and ethical cost.

The European Union Regulation on Clinical Trials will do a lot to ensure that more information on clinical trials conducted in Europe is available to citizens. We welcome the good progress made by amendments added by the ENVI committee which we believe improves the Commissions proposal. We urge you to support the important amendments that will strengthen this further.

The amendments we especially urge you to support are:

- Amendment 30 and amendment 250 which say that data in clinical trial reports should not be considered commercially confidential. These amendments would ensure that commercial considerations don't override the interest in public health research.
- Amendment 193 and 253 which would ensure that if a clinical study report is produced about a clinical trial, it should be made publicly available.
- Amendment 191 which would ensure that clinical trials are registered before they commence.

[2] Moore, T (1995) Deadly medicine. New York; Simon and Schuster

Amendment 30 and amendment 250

Amendment 30 adds new recital 20 which states that clinical study reports are not commercially confidential. Amendment 250 adds Article 78, paragraph 3, sub-paragraph 1 a (new) which sets out the primacy of public health considerations.

Clinical trial information is generated by citizen's participation in trials and should be used to benefit society. Commercial concerns should not override the public interest in making clinical trial information available.

These amendments would bring European law into line with the European Medicines Agency's policy that information in clinical study reports should not be considered commercially confidential. And with the European Ombudsman's decision in November 2010 that the information in trial protocols and clinical study reports should not be considered commercially confidential once a marketing authorisation has taken place.

The definition of what is commercially confidential should be in accordance with EMA guidelines.

A number of pharmaceutical companies including GlaxoSmithKline, Roche and LEO Pharma have committed to making clinical study reports they hold from past trials and will produce in future trials publicly available.

Amendment 30 : New recital 20 (a)		
Text proposed by the Commission		**New recital proposed by the ENVI Committee (June 2013)**
		(20a) According to the policy of European Medicines Agency on access to documents, the Agency releases documents submitted as part of applications for marketing authorisation, including clinical trial reports, on request once the decision-making process for the medicinal product in question has been completed. Furthermore, the Agency continues to extend its transparency policy to proactive publication of clinical trial data for medicinal products once the decision-making process on an application for a Union-wide marketing

		authorisation has been completed. Those standards on transparency and access to documents should be upheld and reinforced. For the purposes of this Regulation, in general the data included in clinical study reports should not be considered commercially confidential once a marketing authorisation has been granted or the decision-making process on an application for marketing authorisation has been completed.

Amendment 250: The primacy of public health considerations

Proposal for a regulation **Article 78 – paragraph 3 – sub-paragraph 1 a (new)**		
Text proposed by the Commission		**Proposal by the ENVI Committee (June 2013)**
		The definition of what is considered as commercially confidential shall be in accordance with Agency guidelines and shall not be allowed to override the interest of public health research.

Amendment 193 and amendment 253

Amendment 193 amends and adds paragraphs 3 and 3a to Article 34 and states that clinical study reports should be published 30 days after marketing authorisation has been granted. Amendment 253 adds new paragraph to Article 78 and sets out public access to clinical study reports.

The Commission's proposed Regulation requires that a summary of the results from clinical trials is published within a year of the trial's end. This summary is usually a short document setting out the protocol, methods, statistical analysis and summary results of what was found. Clinical study reports (CSRs) are much longer documents normally produced for marketing authorisation purposes. CSRs contain a large amount of detailed information about the methods, analysis, results and conclusions of a clinical trial – information that is needed to make and to scrutinise decisions about medicines and to assess published summary findings. A study by researchers at Germany's Institute for Quality and Efficiency in Health Care in October 2013 found that CSRs contain significantly more of the information on patient outcomes in trials that regulators and doctors need to be able to make fully informed choices about how to treat their patients. They have called for CSRs from past and future trials to be made publicly available.

Amendments 193 and 253 would mandate that CSRs, where they are produced, are made publicly available. These amendments would bring the law into line with the European Medicines Agency's policy to proactively make public all CSRs it holds from January 2014.

Amendment 193 also calls for a lay summary of the results of a trial to be publicly available alongside the summary of results published one year after the termination of the trial. We support this.

Amendment 193: clinical study report to be published 30 days after Marketing Authorisation

Proposal for a regulation **Article 34 – paragraphs 3 and 3 a**		
Text proposed by the Commission		**Proposal by the ENVI Committee (June 2013)**
3. Within one year from the end of a clinical trial, the sponsor shall submit to the EU database a summary of the results of the clinical trial. However, where, for scientific reasons, it is not possible to submit a summary of		3. ***Irrespective of the outcome of the clinical trial***, within one year from the end of a clinical trial or ***from its early termination***, the sponsor shall submit to the EU database a summary of the results of the clinical trial ***in accordance with Annex IIIa. It shall be***

the results within one year, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with an explanation.		***accompanied by a summary presented in terms that are easily understandable to a layperson.*** However, where, for ***justified*** scientific reasons, it is not possible to submit a summary of the results within one year, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a ***justification.*** ***In addition to the summary of the results, where the trial was intended to be used for obtaining a marketing authorisation for the investigational medicinal product, the sponsor shall submit to the EU database the clinical study report 30 days after the marketing authorisation has been granted, the decision-making process on an application for a marketing authorisation has been completed, or the sponsor has decided not to submit an application for marketing authorisation.*** ***In the event of non-compliance by the sponsor with the obligations referred to in this paragraph, financial penalties shall be imposed on the sponsor by the Member States concerned. The penalties shall be effective, proportionate and dissuasive.*** ***3a. The Commission shall be empowered to adopt delegated acts in accordance with Article 85 in order to define the***

		content and structure of the layperson's summary. ***The Commission shall be empowered to adopt delegated acts in accordance with Article 85 in order to establish rules for the communication of the clinical study report.*** ***For cases where the sponsor decides to share raw data on a voluntary basis, the Commission shall produce guidelines for the formatting and sharing of those data.***

Amendment 253: Access to clinical study reports

Proposal for a regulation **Article 78 – paragraph 7 a (new)**		
Text proposed by the Commission		**Proposal by the ENVI Committee (June 2013)**
		7a. Free and convenient access to clinical data held in the Agency's database, particularly to clinical study reports, shall be granted to the public. To this end, a hyperlink shall be included to the clinical study reports of the clinical trials.

Amendment 191

Amendment 191 adds a new paragraph to article 33 and calls for clinical trials to be registered before commencement.

Around half of all clinical trials have not been registered properly and a quarter have not been registered at all. This means that we do not have a full record of all past and ongoing trials. Doctors and regulators do not know what clinical trials have been done, never mind what was found in them. Universal registration of trials is the most important way clinical trials can be made more open to scrutiny. It would give researchers and regulators the potential to scrutinise and chase up results from unpublished trials to get a full picture. Universal registration of trials before the first participant is recruited will reduce, or at least identify, selective reporting of outcomes or changes in study design that occur between initiation of the trial and publication of results. All future trials should be registered in the publicly accessible EU database. This is what amendment 191 proposes.

Proposal for a regulation **Article 33 – paragraph 2 a (new)**		
Text proposed by the Commission		**Proposal by the ENVI Committee (June 2013)**
		2a. Prior to the start, all clinical trials shall be registered in the EU database. Information provided shall include the start date and the end date of the recruitments of subjects.

Amendment 29 and amendment 152

Amendment 29 amends recital 20 and amendment 152 adds a new sub-paragraph to article 25. These amendments would ensure that clinical trial data submitted in support of an application to conduct a clinical trial should be from trials registered in a publicly accessible register.

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Amendment 29 on ensuring an accessible EU clinical trials database

Amendment 29: Recital 20		
Text proposed by the Commission		**ENVI's proposed amendment (June 2013)**
(20) In order to increase transparency in the area of clinical trials, clinical trial data submitted in support of a clinical trial application should be based only on clinical trials recorded in a publicly accessible database.		(20) In order to increase transparency in the area of clinical trials, clinical trial data submitted in support of a clinical trial application should be based on clinical trials recorded in a publicly and ***easily*** accessible ***database without imposing any cost on the access to the database. Clinical trial data based on clinical trials conducted before the date of application of this Regulation should be registered in a public register which is a primary or partnered registry of the international clinical trials registry platform of the World Health Organisation.***

Amendment 152: Public register compatibility with WHO registry platform

Proposal for a regulation Article 25 – paragraph 6 – subparagraph 1 a (new)		
Text proposed by the Commission		**Proposal by the ENVI Committee (June 2013)**
		Clinical trial data based on clinical trials conducted before ... [date of application of this Regulation] shall be registered in a public register which is a primary or partnered registry of the international clinical trials registry platform of the World Health Organisation.

Amendment 35

Amendment 35 adds a new recital 25a.

Amendment 35 states that all clinical trials should be registered and a summary of results reported. We support this. Amendment 35 also states that the commission should provide guidelines for the management of and the facilitating of sharing of raw data from all clinical trials. We support this. Many discussions are taking place among companies and academic groups on setting up infrastructures to share patient level clinical trial data with researchers and regulators and the European Medicines Agency has produced a draft policy on clinical trial data sharing.

Amendment 35: new recital 25a		
Text proposed by the Commission		**Proposal by the ENVI Committee (June 2013)**
		(25a) For the sake of transparency, sponsors should submit the summary of the results of a clinical trial together with a layperson's summary, and, where applicable, the clinical study report, within the deadlines and in the format specified by this Regulation. The power to adopt delegated acts in accordance with Article 290 of the Treaty on the functioning of the European Union should be delegated to the Commission in respect of on the preparation of the layperson's summary and the communication of the clinical study report. The Commission should provide guidelines for the management of, and the facilitating of sharing of raw data from all clinical trials.

Amendment 194

Amendment 194 amends paragraph 4 of article 34 to ensure that if a clinical trial is terminated that information is made available and results from the trial, even if incomplete, are submitted to the EU database within 12 months. Publication of all results will reduce reporting biases and help researchers and policymakers produce more reliable systematic reviews of the safety and effectiveness of medical interventions. Publishing results fulfils clinical trialists' ethical responsibility to patients in clinical trials, as set out in the Helsinki Declaration.

Proposal for a regulation **Article 34 – paragraph 4**		
Text proposed by the Commission		**Proposal by the ENVI Committee (June 2013)**
4. For the purpose of this Regulation, if a suspended or temporarily halted clinical trial is not restarted, the date of the decision of the sponsor not to restart the clinical trial shall be considered as the end of the clinical trial. In the case of early termination, the date of the early termination shall be considered as the date of the end of the clinical trial.		4. For the purpose of this Regulation, if a suspended or temporarily halted clinical trial is not restarted, the date of the decision of the sponsor not to restart the clinical trial, ***extended to include the period during which the subjects are subject to monitoring under the terms of the protocol***, shall be considered as the end of the clinical trial. In the case of early termination, the date of the early termination shall be considered as the date of the end of the clinical trial. ***After 12 months of temporary halt, the data from the clinical trial shall be submitted to the EU database, even if incomplete. The reasons for early termination of a clinical trial shall be published in the EU database.*** ***If a clinical trial is discontinued, the sponsor shall notify the reasons thereof to the Member State concerned through the EU portal within 15 days from the decision***

		to discontinue the clinical trial.

Amendment 247

Amendment 247 and 248 set out the purpose of the EU clinical trials database's public and citizen purpose.

Clinical trial information is only generated by the participation of millions of citizens who have volunteered for clinical trials. We support the proposal that publicly available information contained in the database shall contribute to protecting public health and fostering the innovation capacity of European medical research, while recognising the legitimate economic interests of sponsors.

Amendment 247: EU database's public and citizen purpose

Proposal for a regulation **Article 78 – paragraph 2**		
Text proposed by the Commission		**Proposal by the ENVI Committee (June 2013)**
2. The EU database shall be established to enable the co-operation between the competent authorities of the Member States to the extent that it is necessary for the application of this Regulation and to search for specific clinical trials. It shall also enable sponsors to refer to previous submissions of an application for authorisation of a clinical trial or a substantial modification.		2. The EU database shall be established to enable the co-operation between the competent authorities of the Member States to the extent that it is necessary for the application of this Regulation and to search for specific clinical trials. ***It shall also enable sponsors to refer to previous submissions of an application for authorisation of a clinical trial or a substantial modification. It shall also enable citizens of the Union to have access to clinical information, in easily searchable form, about medicinal products in order to enable them to make informed decisions about their health.*** ***Publicly available information contained in***

		the database shall contribute to protecting public health and fostering the innovation capacity of European medical research, while recognising the legitimate economic interests of sponsors.

Amendment 248: EU database's public and citizen purpose

Proposal for a regulation **Article 78 – paragraph 3 – introductory wording**		
Text proposed by the Commission		**Proposal by the ENVI Committee (June 2013)**
3. The EU database shall be publicly accessible unless, for all or parts of the data and information contained therein, confidentiality is justified on any of the following grounds:		3. The EU database shall be publicly accessible ***in accordance with Regulation (EC) No 1049/2001*** unless, for all or parts of the data and information contained therein, confidentiality is justified on any of the following grounds:

Amendment 290

A summary of results should be made publicly available within one year of the end of all clinical trials, and the Commission's proposed Regulation calls for this. Amendment 290 introduces a new Annex IIIa which sets out what should be included in this summary of results. We support this list. Results to be uploaded in a format that allows the main reported items to be searchable and enables sharing of information between registries.

Proposal for a regulation **Annex III a (new)**		
Text proposed by the Commission		**Proposal by the ENVI Committee (June 2013)**
		Annex IIIa ***Content of the summary of the results of clinical trials*** ***The summary of the results of the clinical trials referred to in Article 34(3) shall contain information on the following elements:*** ***1. Trial information:*** ***a) Study identification*** ***b) Identifiers*** ***c) Sponsor details*** ***d) Paediatric regulatory details*** ***e) Result analysis stage*** ***f) General information about the trial including: a structured summary of trial design, methods, results, and conclusions; scientific background and explanation of rationale; specific objectives or hypotheses*** ***g) Population of trial subjects with actual number***

		of subjects included in the trial and the eligibility criteria ***2. Subject disposition with sufficient details to allow for replication, including:*** ***a) Recruitment*** ***b) Pre-assignment Period*** ***c) Post Assignment Periods*** ***3. Baseline Characteristics:*** ***a) Baseline Characteristics (Required)*** ***Age*** ***b) Baseline Characteristics (Required)*** ***Gender*** ***c) Baseline Characteristics (Optional)*** ***Study Specific Characteristic*** ***4. End Points:*** ***a) Endpoint definitions*** ***b) End Point #1**** ***Statistical Analyses*** ***c) End Point #2,*** ***Statistical Analyses*** ****Information shall be provided for as many end points as defined in the protocol.*** ***5. Adverse Events:*** ***a) Adverse events information*** ***b) Adverse event reporting group*** ***c) Serious Adverse Events*** ***d) Non-serious adverse event*** ***6. More Information:***

		a) Global Substantial Modifications ***b) Global Interruptions and re-starts*** ***c) Limitations, addressing sources of potential bias and imprecisions, & Caveats*** ***7. The protocol and its subsequent modifications.***

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The organisations associated with this briefing are willing, able and enthusiastic to meet with and brief any interested parties about the issues described in this document.

We are also keen to hear from other organisations who would like to add their signature to this briefing document before it is sent out again ahead of final discussions on 12th December 2013.

In both instances, please contact as above.

About the AllTrials campaign

The AllTrials campaign was launched in January 2013 to call for all clinical trials to be registered and results reported. It is supported by 60,000 people and more than 400 organisations worldwide, including pharmaceutical companies, regulators, medical and scientific bodies, Universities, research funders and more than 150 patient groups. www.alltrials.net

About the European Association of Hospital Pharmacists

The European Association of Hospital Pharmacists is an association of national organisations in 34 countries representing hospital pharmacists at European and international levels. It represents and develops the hospital pharmacy profession within Europe in order to ensure the continuous improvement of care and outcomes for patients in the hospital setting. This is achieved through science, research, education, practice, as well as sharing best-practice and responsibility with other healthcare professionals. www.eahp.eu

About the European Patients' Forum

The European Patients' Forum is an umbrella organisation that works with patients' groups in public health and health advocacy across Europe. Their members represent specific chronic disease groups at EU level or are national coalitions of patients. Their mission is to ensure that the patients' community drives policies and programmes that affect patients' lives to bring changes empowering them to be equal citizens in the EU. EPF helps to empower patients' organisations through educational seminars, policy initiatives and projects. They coordinate best practice exchanges between patient organisations at European and national levels. Their programmes also help to strengthen their organisational and advocacy capacity. www.eu-patient.eu

About the European AIDS Treatment Group

The European AIDS Treatment Group (EATG) is a European network of nationally-based volunteer activists comprising of more than 110 members from 40 countries in Europe. Their members are representatives of different communities affected by HIV/AIDS in Europe. Since its foundation, the EATG has been at the forefront of the development of the civil society response to the HIV/AIDS epidemic in Europe. It represents and defends the treatment-related interests of people living with HIV/AIDS. Their activities focus on treatment literacy and treatment advocacy. A major goal for EATG when it was founded in 1992 was the simultaneous development of therapies in Europe, including not only antiretroviral therapies, but as well as treatments for opportunistic infections and other AIDS related conditions. www.eatg.org