Brussels, 7 May 2013

Letter to MEPs members of
the ENVI, ITRE and IMCO Committees

Clinical Trials Regulation (amendment analysis): Not knowing = HARM!

Dear Member of the European Parliament,

The **Clinical Trial Regulation** is currently being discussed (vote in ENVI Committee on 29 May 2013). As patients, researchers, doctors, scientists and civil society representatives we would like to draw your attention not only to the dangers it encompasses but also to the opportunities it brings along.

DANGERS:

Confusing new definitions, including that of 'Low-intervention' clinical trials, risk turning European citizens into guinea pigs without asking for prior consent

In many cases (rare diseases, cancer treatment, marketing authorisation given under exceptional circumstances or under conditions), marketing authorisations are granted for medicines when sufficient evidence about their efficacy and safety is not yet available, **thus requiring post-efficacy and post-safety trials to be conducted to complete the evaluation.**

According to the new definition proposed by the European Commission, a 'low-intervention' clinical trial would also include post-authorisation efficacy and safety studies since authorised medicinal products are tested in accordance with their marketing authorisation (**a**).

This measure endangers participants since:

- trial sponsors would be exempted from the obligation to compensate participants for any damage suffered by subjects in 'low-intervention' clinical trials;
- regulatory authorities would have less time for approval of trial applications;
- the requirements to report adverse drug reactions would be less stringent.

In order to maintain the protection of clinical trial participants, we call on you to support the following amendments (AM):

- *On the definition of a clinical trial*: AM 182 and AM 186

These two amendments reintroduce the more comprehensive definition of Directive 2001/20/EC and thereby prevent certain interventional clinical trials from being labelled as "clinical studies" and from falling outside the scope of the Clinical Trials Regulation;

- ***On the definition of a 'low-intervention" clinical trial*: AM 185**

-- AM 185 includes "post-marketing safety or post-marketing efficacy trials on a medicinal product authorised within the last 10 years" in the definition of a 'clinical trial'. This inclusion is consistent both with medicinal products' regulation (a marketing authorisation is reviewed within 5 years from approval and only considered unlimited after a minimum of 10 years (Art. 24 of Directive 2001/83/EC) and with the recently adopted pharmacovigilance legislation (**b**)); it is also consistent with the OECD classification (**c**).

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a- For example, the REGULATE study of benfluorex (Mediator°) and the VIGOR study of rofecoxib (Vioxx°) would fall into this category since the authorised medicinal products were tested in accordance with their marketing authorisation.

b- 'Low-intervention' clinical trials should not include medicinal products under additional monitoring as defined by the new pharmacovigilance legislation adopted in 2010 (these medicines are identified by a black triangle pointing downwards and concern

OPPORTUNITY:
Choose transparency to protect public health

At present, half of all clinical trials are never published. Of those that are published, only a selection of positive results is disclosed and important harms are often omitted.

Numerous recent drug disasters would have been avoided if public access to clinical data had been publicly accessible. In fact, disclosing key information allows timely and independent data reanalysis (scrutiny by the scientific community).

In order to protect public health, we urge you to support amendments that require the public disclosure of a complete clinical study report (CSR) as outlined by ENVI rapporteur MEP Glenis Willmott (**support AMs 21 and 59**):

- Public disclosure of clinical trials data is in the direction of history. The Clinical trials Regulation could represent a historic move towards better science and ultimately better therapy and less harm for patients;
- It would moreover give legal certainty to the European Medicines Agency (EMA) with the implementation of its 2010 policy to widen public access to documents.

And we ask you to reject amendments strengthening the protection of so-called "commercially confidential" or "commercially sensitive" information which – if adopted - would be a major step back and undermine the accountability of the European pharmaceutical regulatory system (**reject AMs 120, 166, 169, 539, 667, 668, 669**).

Our joint letter "Clinical Trials Regulation – Protect public health: Choose transparency!" outlines:

- Why the publication of the summary of clinical trial results is not enough; and
- How the disclosure of detailed clinical data (raw data or in Clinical study report (CSR) format) helps to advance biomedical research (**d**).

Opponents to transparency are invoking **obstacles, which are but a long list of red herrings**.
Please find attached our one page briefing paper "Debunking secrecy myths which hinder transparency", which answers the following questions:

1- Are clinical trials data "commercially confidential" data?;
2- Does the disclosure of clinical trials data put patients confidentiality at risk?;
3- Does clinical trials data disclosure represent an added burden for academics or non-commercial researchers?;
4- Will clinical trials data be misinterpreted and will that scare the public?

Please find also below (in Appendix) an **analysis of the key positive amendments to be supported, as well as a list of worrying amendments to be rejected**.

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new active substances, medicinal products which were granted marketing authorisation in exceptional circumstances conditionally despite insufficient evaluation) (recital 10 of Directive 2010/84/EC).

c- The OECD classification specifies: "*the following product-related modulating factors [should be taken into account] when assigning one of the above categories (…) as they may impact the risk assignment (…):*

- *"novelty of the medicinal product and/or of its class (including new formulation of a marketed substance";*
- *"innovative nature of the treatment (e.g. advanced therapy/biologics) (…)*"

("OECD recommendation on the governance of clinical trials" http://www.oecd.org/sti/sci-tech/oecd-recommendation-governance-of-clinical-trials.pdf).

d- The Joint Letter is available at: **http://www.isdbweb.org/publications/download/175**.
It has been endorsed by AGE Platform Europe, Association Internationale de la Mutualité (AIM), the Cochrane Collaboration, the European AIDS Treatment Group (EATG), the European Social Insurance Platform (ESIP), Health Action International (HAI) Europe, the International Society of Drug Bulletins (ISDB), the Medicines in Europe Forum (MiEF), PLOS Medicine, the TransAtlantic Consumer Dialogue (TACD) and WEMOS.

We have also prepared a voting list analysing all the amendments under discussion. Should you be interested in receiving a copy, please contact Teresa Alves at talves@prescrire.org .

We remain at your disposal for any questions you might have. We hope that you will consider recommendations into consideration.

Kind Regards,

Medicines in Europe Forum (MiEF)

International Society of Drug Bulletins (*ISDB*)

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Appendix
Clinical trials regulation - analysis of key amendments

Positive amendments: to be supported

We ask you to support amendments that uphold patients' safety and protect public health, namely:

Article of the Regulation	Number of the AM	Content of the AM
Recital 2	2	Demands prior approval of a clinical trial by an ethics committee
Recital 59 a new	173	Enshrines right of access to documents (Charter of fundamental rights of the EU)
Article 2 – paragraph 2 – point 1 – introductory part	182	Reintroduces the definition of a clinical trial from Directive 2001/20 EC, by replacing the term clinical study by clinical trial.
Article 2 – paragraph 2 – point 1 – point c a new	185	Includes post-marketing efficacy and safety studies into the definition of a clinical trial.
Article 2 – paragraph 2 – point 2	186	Deletes proposed definition of a clinical trial, which is too restrictive and confusing.
Article 2 – paragraph 2 – point 6 a new	219	Introduces concept of best current proven intervention, in line with the Helsinki declaration.
Article 2 – paragraph 2 – point 20	237	Redefines notion of protocol to also include other relevant documents, such as successive versions and amendments.
Article 2 – paragraph 2 – point 30 a (new)	21	Defines notion of Clinical Study Report.
Article 2 – paragraph 2 – point 30 b	241	Adds to the notion of Clinical Study Report.
Article 5 – paragraph 5 a new	286	Requires the assessment report to be submitted through the EU portal and be made publicly available.
Article 6 – paragraph 5	320	Requires Member States considerations to be included in the assessment report, and in case they differ from the reporting Member State's assessment, to indicate the reasons thereof.
Article 11	387	Deletes provisions that separate ethical from scientific assessment.

Article of the Regulation	Number of the AM	Content of the AM
Article 15	409	Requires substantial modifications to the protocol to be authorised by an independent ethics committee, prior to their implementation.
Chapter IV a new	446	Enshrines regulation No.1049/2001 and public access to clinical study reports through hyperlink in database.
Article 34 – paragraph 3	51	Requires the submission of the clinical study report and its lay summary to the EU database within one year of completion of the trial.
Article 46 a new	584	Requires all new interventions to be tested against the best current proven intervention (also includes exceptions).
Article 49 – paragraph 2	59	Specifies the clinical study report as the format for disclosure of clinical trial information.
Article 53 – paragraph 1	597	Requires all clinical study reports submitted to be easily searchable and publicly available online.
Article 78 – paragraph 3 – indent 3	666	Deletes provisions that hinder public access to the database, or independent researchers to analyse results.
Annex I – point 13 – indent 8 a new	71	Demands submission of full statistical analysis plan, which ensures research robustness and prevents data manipulation.
Annex I – point 53 b (new)	74	Requires information and informed consent forms to be reviewed by patients prior to be submission.

Hazardous amendments: to be rejected

We would like to highlight the problematic amendments, which we consider to be hazardous to patient safety and public health.

Article of the Regulation	Number of the AM	Content of the AM
Recital 3a new	84	Excludes non-interventional studies, among which post-authorisation safety studies (conducted to complete a drug's evaluation), from the scope of the regulation. This would cart off access to valuable scientific data.
Recital 8	90	Enforces the tacit authorisation procedure when Member States do not meet set deadlines, even when ethical issues are at stake.
Recital 20 a new	120	Hinders access to information by considering all clinical data to be commercially confidential before a marketing authorisation has been obtained, and some sections also after approval – a major backtrack from the current situation and from the European Medicines Agency's 2010 policy to widen public access to documents.

Article of the Regulation	Number of the AM	Content of the AM
Recital 23	126	Establishes unclear/vague exceptions to the informed consent procedure.
Recital 52	166	Limits scope of database, by stating that it should not hamper the protection of commercial interests, including Intellectual Property Rights. Specifically established commercially confidential information not to be disclosed.
Recital 52 a new	169	Invokes the protection of commercially confidential information in order to avoid harming competitive position of sponsors.
Article 29 – paragraph 3 a new	473	Establishes exceptions to the informed consent procedure.
Article 33 – title	517	Deletes notification of the end of the subjects' recruitment period, which is worrying as it can affect the protocol and influence trial results.
Article 34 – paragraph 3 – subparagraph 2 a new	539	Limits access to data, by invoking protection of commercial confidentiality information. Requires summaries of results (not full Clinical Study Reports) to be public one month after marketing approval of the drug, or in case of non-approval up to one year.
Article 73	632	Deletes the national indemnification mechanism.
Article 78 – paragraph 3 – indent 3 a new	667	Invokes the protection of commercially confidential information, in detriment of access to data.
Article 78 – paragraph 3 a new	668	Introduces the summary of results as the format for disclosure of clinical trial information.
Article 78 – paragraph 5	669	Limits access to data, states that no commercially confidential information or information undermining Intellectual Property Rights should be publicly available.

A full voting list analysing all amendments is available upon request

We have prepared a voting list analysing all the amendments under discussion, guided by the following principles:
- Upholding ethics, in accordance with the Helsinki Declaration;
- Ensuring maximum transparency and minimum conflicts of interest in clinical research;
- Protecting patients and clinical trial participants by ensuring maximum safety;
- Enabling thoughtful review by member states by increasing response timelines;
- Upholding the safety of trial participants and the integrity of clinical research by avoiding tacit agreement;
- Minimizing the delegation of important responsibilities from the investigator to other parties.

Should you be interested in receiving a copy, please contact Teresa Alves at talves@prescrire.org