



Brussels, 2 December 2013  
**Joint letter to Member States'  
Permanent Representatives (CoRePers)**

## **EU Regulation on clinical trials: The protection of clinical trial participants must not be undermined**

**We call upon the Council and MEPs to:**

- ensure that the new Regulation does not weaken the rights of clinical trial participants
- make sure that Member States uphold their responsibility and sovereignty in assessing the acceptability of clinical trials.

Several measures contained in the July 2012 EU Commission's proposal for a new Regulation on clinical trials aim to deregulate clinical research in human subjects, thereby undermining Member States' subsidiarity on ethical matters <sup>(1)</sup>.

We welcome the improvements made by the ENVI Committee of the European Parliament and the Council so far. We particularly welcome the efforts made to limit the undermining of the protection of clinical trial participants, particularly by **restoring the role of national Ethics Committees** - the corner stone of Directive 2001/20/EC.

In addition, **we welcome the Council improvements to the ENVI Committee report:**

- **Refusing the tacit approval procedure** as proposed by the European Commission; no trial should be authorised in a Member State's own territory without a proper review by their national Ethics Committee. A proper review also entails that Ethics Committees and Member States staff have **sufficient time** to allow for a sound assessment of the applications;
- **Reinstating a clearer definition of the notion of Clinical trial**, to prevent some trials from being considered "non-interventional studies" by default;
- Refusing the proposal that patients can be asked to provide "broad consent" or that patients can be included in "low-intervention trials" without having given their informed consent;
- Ensuring that "low-intervention clinical trials" are subject to the same application procedure as any other clinical trial <sup>(2)</sup>.

**Our additional recommendations to safeguard protection of clinical trial participants include:**

- 1. Making clear that Ethics Committees' opinions are binding** as it was foreseen by Directive 2001/20/EC; Member States should have the possibility to opt-out if their national Ethics Committee is against the conduct of the clinical trial on their territory;

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1- For more details, read our joint analysis ("New Proposal for a Regulation on Clinical Trials – Joint analysis" 5 February 2013 : 12 pages.), available at: <http://english.prescrire.org/en/79/207/46302/2507/2506/SubReportDetails.aspx>

2- We also welcome the Council support of the provision of the ENVI Committee report that "*The subjects participating in a clinical trial should represent the population groups (e.g. gender and age groups) that are likely to use the medicinal product investigated in the clinical trial*". However, we would advise to **delete "unless otherwise justified in the protocol"**, since it opens the door to establishing exceptions which will not improve current practice (item 20 of the Council working document Part 1).

2. **Ensuring the independence of evaluation committees:** Drug Regulatory Agencies provide scientific advices to pharmaceutical companies who seek for them and who pay fees in exchange for them. This practice leads to Drug Regulatory Agencies becoming “scientific co-developer” of the medicine. Therefore, Ethics Committees have to be hierarchically independent from Drug regulatory agencies in order to guarantee the independence of their opinion and prevent them from conflicting interests. Moreover, the ENVI Committee amendment requiring that “*Names, qualifications, and declaration of interest of the persons assessing the application should be made publicly available*” should be reinstated (**amendment 25 of ENVI Report** (recital 14); item 28 of the Council working document).
3. **Refusing to include “off label use” into the definition of “low-intervention trials”** even under the condition that “*its use is an evidence based treatment supported by published scientific evidence on safety and efficacy*” (item 11 (recital 9) of Council working document). This provision is very dangerous:
  - evidence shows that many publications and especially guidelines produced by “experts” are biased, due to conflicts of interest;
  - the risk is that manufacturers would first be encouraged to seek marketing authorisation for a narrow therapeutic indication, which would be granted based on evidence from small short-term standard clinical trials, since it would concern few patients. Then, the manufacturer will have an interest in stimulating off-label use to gather scientific evidence on the safety and efficacy of that particular medicine when used according to those off-label indications. Ultimately, such a provision would entitle the manufacturer to ask for an extension of the marketing authorisation based on less rigorous “low-intervention trials”.
4. **Ensuring that all clinical trial participants are eligible for compensation in case of damages, including in “low-intervention trials”** (in fact, post-authorisation safety studies are conducted when there are concerns about adverse drug reactions).  
In Chapter XII, the Commission proposed a harmonised approach with the setting up of a “*national indemnification mechanism*”. The Council considers that participants’ compensation is a Member State prerogative and only requires an “*arrangement, which is appropriate to the nature and the extent of the risk*”. Such a measure produces too much wiggle room for interpretation and triggers competition among Member States. The risk is that, in order to attract clinical trials, this competition would lead to the lowest common denominator in damage compensation (items 58 to 62 of the Council working document);
5. **Demand investigators (clinicians) – not sponsors – to report to health authorities ALL serious adverse reactions, whether “expected” or not <sup>(3)</sup>. At the very least, support amendment 75 of the ENVI Committee**, which includes into the definition of serious adverse events also other events deemed serious by the investigator in the context of the clinical trial.
6. **Reinstate provisions from Directive 2001/20/EC** which establish that:
  - in case of death of a subject, sponsors are required to supply health authorities with any additional information that they may request (**article 16(3) and (4) of Directive 2001/20/EC**);
  - toxicological experiments must take place prior to any use of the product on humans (**recital 2 of Directive 2001/20/EC**);
7. **Support amendment 66 of the ENVI Committee to the definition of substantial modification** in order to include any modifications likely to change the interpretation of the scientific documents used to support the conduct of the clinical trial, or any other change to any aspect of the clinical trial that is otherwise significant;

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<sup>3</sup> - The Regulation and item 53 of the Council working document only require the trial sponsor to report **serious** adverse drug reactions to health authorities if these are “**unexpected**”.

8. **Reinstate clear deadlines for serious ADR reporting by the sponsor to health authorities** (support **amendments 38 and 39** of the ENVI Committee (items 47 and 48 of the Council working document part 1)) **and reinstate clear deadlines for the reporting of serious breaches to the rules in the conduct of a clinical trial** (item 52 of the Council working document part 1); such timelines were also stated in Directive 2001/20/EC.

**On the issue of transparency, we have already called for the Council to support and strengthen ENVI's Report improvements** <sup>(4)</sup>. We invited the Council to support particularly **amendments 30 & 193** (about clinical study reports not to be considered commercially confidential), **amendment 194** and **amendment 253**.

We have also called for the Council to request:

- The publication of clinical study reports within 3 years after the end of a clinical trial, at the latest, if the sponsor has not by then applied for marketing authorisation. This would ensure that these results are not forever lost;
- To clearly state that the following information is not to be considered commercially confidential: clinical trial data, the reasons for temporary halt and early termination of a trial, as well as regulatory documents concerning the criteria and decision about a trial's authorisation and a medicine's marketing authorisation.

**We also call on the Council to reinstate the following amendments adopted in ENVI Committee:**

- A **Universal Trial Registration Number (UTRN)** should be assigned to each trial in order to allow effective following of the trial (from initial ethical approval to final publication) (**amendment 20** of ENVI report; item 23 of the Council working document);
- The **reasons for withdrawing of a clinical trial** should be notified via the EU portal (amendment 28 of ENVI report; item 31 of the Council working document);
- **Dissuasive and harmonised sanctions should be applied by Member States** in case of failure to make clinical trial publicly available within the defined timelines.

In addition, in regards to the submission by the sponsor of a *"summary of the results of the clinical trial within the defined timelines"*, we call on the Council to **delete the exception that establishes that *"due to scientific reasons (e.g., when the clinical trial is still ongoing in third countries and data from that part of the trial are not available)"*** manufacturers would be able to delay publication. When a "clinical trial is still ongoing in third countries", preliminary results for other sites should nonetheless be made available within the defined timelines in order to prevent any undue postponement.

We sincerely hope that you will take our recommendations into account. Should you have any queries, please do not hesitate to contact us.

**Association Internationale de la Mutualité (AIM)**  
**Health Action Internationale (HAI) Europe**  
**International Society of Drug Bulletins (ISDB)**  
**Medicines in Europe Forum (MiEF)**  
**WEMOS**

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4- Our 18 November 2013 joint open letter (AIM, HAI Europe, ISDB, MiEF, Nordic Cochrane Centre, TACD) "An urgent call for support to clinical data transparency" is available here:

<http://english.prescrire.org/en/79/207/46302/3053/2506/SubReportDetails.aspx>

## Endorsing organisations

**AIM.** The Association Internationale de la Mutualité (AIM) is a grouping of autonomous health insurance and social protection bodies operating according to the principles of solidarity and non-profit-making orientation. Currently, AIM's membership consists of 41 national federations representing 29 countries. In Europe, they provide social coverage against sickness and other risks to more than 150 million people. AIM strives via its network to make an active contribution to the preservation and improvement of access to health care for everyone. More info: [www.aim-mutual.org](http://www.aim-mutual.org). Contact: [corinna.hartrampf@aim-mutual.org](mailto:corinna.hartrampf@aim-mutual.org).

**HAI Europe.** Health Action International (HAI) Europe is a non-profit, European network of consumers, public interest NGOs, health care providers, academics, media and individuals working to increase access to essential medicines and improve their rational use through research excellence and evidence-based advocacy. More info: [www.haieurope.org](http://www.haieurope.org). Contact: [ancel.la@haieurope.org](mailto:ancel.la@haieurope.org)

**ISDB.** The International Society of Drug Bulletins, founded in 1986, is a worldwide network of bulletins and journals on drugs and therapeutics that are financially and intellectually independent of the pharmaceutical industry. Currently ISDB has about 80 members representing 41 countries around the world. More info: [www.isdbweb.org](http://www.isdbweb.org). Contact: [press@isdbweb.org](mailto:press@isdbweb.org).

**MiEF.** The Medicines in Europe Forum (MiEF) was launched in March 2002 and reaches 12 European Member States. It includes more than 70 member organizations representing the four key players on the health field, i.e. patients groups, family and consumer bodies, social security systems, and health professionals. Such a grouping is unique in the history of the European Union and is testament of the importance of European medicines policy. Contact: [pierrechirac@aol.com](mailto:pierrechirac@aol.com)

**Wemos.** Wemos influences international policy in such a way that the right to health is respected, protected and promoted. In doing so, Wemos devotes special attention to vulnerable sections of society. Wemos advocates ethical conduct, coherent policy and equal access to care. Its lobbying work focuses on lasting improvements in Dutch, European and global policy. More information: [www.wemos.nl](http://www.wemos.nl). Contact: [annelies.den.boer@wemos.nl](mailto:annelies.den.boer@wemos.nl)