HAI EUROPE RESPONSE

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This response has been prepared by Health Action International (HAI) Europe. HAI Europe is a non-profit, European network of consumers, public interest NGOs, health care providers, academics, media and individuals with over 25 years experience in representing the voice of civil society, and poor and marginalised people in medicines policy debates.

Our authority rests on our integrity and independence from commercial and political party interests, our research excellence and evidence-based advocacy.

- HAI advocates for access to essential treatments that satisfy the priority health care needs of a population.
- HAI Europe promotes better access to medicines by advocating for EU trade policies that are coherent with the EU's commitments on health and development; by campaigning for changes to the EU's internal market laws that hamper access to medicines in Europe; by advancing EU actions on the exploration of new models of medical innovation.
- HAI Europe is committed to ensuring the rational use of medicines through greater controls on medicines promotion, independent medicines information, greater patient involvement in the reporting of adverse drug reactions so that harmful or ineffective medicines are identified more quickly, thereby reducing the threat to public health.
- HAI Europe advocates for the highest levels of transparency, independence and accountability in all aspects of pharmaceutical policy and regulation, as well as the wider participation of patients and consumers in decisions that will affect their health and wellbeing.

Summary

HAI Europe welcomes the opportunity to respond to the consultation on the European Commission's Concept Paper on the Clinical Trials Directive. We would like to emphasize the importance of simultaneously ensuring the objectivity and robustness of trial data as well as the safety of study participants, particularly by respecting the ethical norms outlined in the Declaration of Helsinki. [4]

Executive Agency for Health and Consumers

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Establish a single submission with a subsequent Coordinated Assessment Procedure (CAP) (point 1.3.1)

Harmonised procedures can greatly reduce the bureaucratic burden on regulatory agencies as well as inconsistent evaluation criteria across different EU Member States. The priority should always be to have the appropriate checks and balances to ensure the highest standards of safety and objectivity in clinical trials. Checks and balances necessitate the administrative process, which should be streamlined so-as not to replicate work.

The single submission with a CAP can address concerns about the need for a common procedure with harmonised ethical standards while limiting the administrative burden. Among the considerations for CAP, a harmonised approach should be adopted for the composition of Ethics Committees and the criteria for evaluating the suitability of the investigator (point 1.3.1.b). As part of the standard procedure, the details of awards and compensation for investigators should be disclosed to all trial participants (point 1.3.1.b). Above all, the criteria applied by Ethics Committees should be harmonised to the highest existing standard. The CAP should always avoid lowering standards to the basic common denominator.

Developing a clarified approach to trial evaluation by a common Ethics Committee would enhance the reliability of the CAP. HAI Europe would welcome the establishment and implementation of detailed rules on a common approach to Ethics Committees in an Annex to the legislation. Points to be considered should include:

- The composition of the Committee,
- The declaration of and handling/resolution of Committee members' conflicts of interest,
- The ethical criteria to be upheld and an explanation of how these will be evaluated, and
- The decision-making structure of the Committee.

Resolve disagreement from the assessment report by making decisions at the EU level (point 1.3.2)

Any disagreements arising from the assessments conducted under CAP would best be resolved by being referred to the EU Commission or the European Medicines Agency (EMA) for a decision at the EU level. This option can best be implemented by developing criteria for deliberating disagreements, by establishing a clear decision-making structure that relies on empirical evidence and by providing an opportunity for input from citizens and healthcare professionals.

Establish a mandatory application of the CAP (point 1.3.3)

The CAP presents an opportunity to adopt the highest existing standards in Clinical Trials assessment as common procedures across Europe. To avoid asymmetries in the implementation of the clinical trials directive across different EU Member States, a mandatory application of the CAP for all clinical trials is necessary.

Clarify the shortened timeline for approval in perceived low-risk situations (point 1.3.4)

HAI Europe is cautious about invoking a shortened timeline for approval when risks to trial subjects are perceived to be low. The EC Directive should clearly identify how such an assessment would take place: how would it be decided whether the risks are low and by whom? Moreover, the legislation should outline how it would be determined whether the proposed trial "*poses only minimal risks to the safety of the trial subject compared to normal clinical practice*." These are key considerations that could open the door to potentially hazardous or unethical practices if not properly regulated from the outset.

*Maintain the definition of 'non-interventional' trials (point 2.1.1)***)**

Non-interventional studies are currently defined as administering a particular medicine to treat the condition it was authorised for, but outside of a study protocol and without additional interventions. With lucrative rewards for trial participants and investigators, as well as relaxed regulatory oversight, non-interventional studies can be used by the manufacturers as marketing tools under the guise of scientific research.[1] The Commission itself noted that non-interventional studies are "*often of poor quality and frequently promotional*."[2] HAI Europe cautions against expanding the definition of 'non-interventional' trials, which could open the door to unethical medicines promotion.

Include clinical trials by 'academic/non-commercial' sponsors in the scope of the Directive (point 2.1.2)

The same ethical principles and procedural requirements should be met by all clinical trial sponsors. It is widely recognised that publicly-funded and/or commercially-independent clinical trials maximize scientific objectivity and public trust in research outcomes. However, overly dissuasive administrative and regulatory burdens may leave academic and non-commercial sponsors, who traditionally have limited resources, with no other choice than to seek company support.[3] Therefore, additional administrative support should be provided for academic and non-commercial sponsors to navigate and comply with the approval process.

Develop precise rules on the content of the CT application dossier and safety reporting (point 2.2)

A single set of rules to be applied across the EU is favourable, provided that these rules embody the highest existing standards of safety and objectivity. HAI Europe strongly urges the Commission to develop these standards and Annexes side-by-side with input from citizens groups and healthcare professionals. We particularly welcome the development of an Annex to

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[1] Kessler D.A., Rose J.L., Temple R.J., Schapiro R. & Griffin J.P. (1994) Therapeutic-Class Wars -- Drug Promotion in a Competitive Marketplace. New England Journal of Medicine. URL: http://www.nejm.org/doi/full/10.1056/NEJM199411173312007

[2] Strategy to better protect public health by strengthening and rationalising EU pharmacovigilance: public consultation on legislative proposals, Brussels, 5 December 2007 (point 3.2.5)

[3] Hemminki A. & Kellokumpu-Lehtinen, P.-L. (2006) Harmful impact of the EU Clinical Trials Directive. British Medical Journal. URL: http://www.bmj.com/content/332/7540/501.full

the legislation outlining the *collection, verification and presentation of adverse reaction reports* (ADR) since there is evidence of underreporting of ADRs in trials.[4]

Ensure informed consent in emergency clinical trials (point 2.6)

Informed consent is a central pillar of ethical clinical trials. Participation should always be voluntary and informed, while giving special protection to vulnerable populations.[5] While emergency clinical trials often need to be undertaken in extenuating circumstances, the principles of informed consent and protection of the vulnerable still need to be respected.

In cases where trial subjects may not be in a state to give their informed consent, one could obtain proxy consent. This can be done by consulting with people who have had a similar condition and asking them if they would have been willing to become trial subjects. In cases where informed consent would be evaluated by an investigator, it is imperative that an external independent investigator consults with the potential trial subject and/or reaches a decision. An independent evaluation limits the potential for a conflict of interest from arising between the primary investigator's award or recognition for conducting the trial, and the best interests of the trial participant(s).

Authorisation process for clinical trials in third countries (point 3)

There are significant challenges to ensuring that good clinical practices (GCP) are respected in trials falling outside the EU's jurisdiction. In 2004, the EC Clinical Trials legislation was adopted, affirming the EU's commitment to ethical conduct in studies conducted at home or abroad. The legislation specifically requires applicants to submit a statement of compliance to GCP. However, this mechanism has been criticized as insufficient and often difficult to evaluate.[6]

It is unacceptable that the current legislation allows data from clinical trials that were not published in a register, simply by submitting an explanation and/or justification. All clinical trials conducted within the EU or in third countries, whose data will be used in a EU market authorisation application, should be included in the EU Clinical Trials Register without exception. Mandatory inclusion in a publicly accessible register increases the transparency of research protocols and outcomes, crucial safety data and ethical considerations, ultimately benefiting public health.

Ethical concerns about market authorisation application with data from clinical trials in third countries (point 3)

European Union legislation, adopted in 2001, identifies that clinical trials conducted in third countries should "*be carried out in accordance with the ethical principles that are reflected... in the Declaration of Helsinki*."[7] However, evidence shows that little attention has been paid to clinical trial ethics in assessments for EU marketing authorisations.[6] For example, trials for antipsychotic medicines unjustifiably used placebos and denied effective first-line treatments to

[4] See Cilostazol in India. Published by the Center for Research in Multinational Corporations (SOMO) in Briefing paper on ethics in clinical trials (2006). URL: http://mvoplatform.nl/publications-nl/Publication_2540-nl/at_download/fullfile
[5] The Declaration of Helsinki developed by the World Medical Association
[6] Ethics for Drug Testing in Low and Middle-Income Countries (2008). Published by the Center for Research in Multinational Corporations (SOMO). URL: http://somo.nl/publications-nl/Publication_2472-nl/at_download/fullfile
[7] Point 8 of the Introduction to the Annex of the Clinical Trials Directive 2001/83/EC

study participants. The data from these trials were later used to obtain market authorisation for the products Abilify (granted by the European Medicines Agency in 2004) and Seroquel (granted by the Medicines Evaluation Board of the Netherlands in 2007).