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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.

HAI Europe welcomes the opportunity to respond to the EMA's reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EMA.

Introduction (Chapter 2)

The EMA aims to strengthen the process of clinical trials conducted in third world countries to assure the trials have been conducted in accordance with the principals of Good Clinical Practice (GCP) and are equivalent to those applied in the EU. HAI Europe is concerned about the significant challenges in ensuring that GCP are respected in trials falling outside the EU's jurisdiction. The EC Clinical Trials legislation was adopted in 2004, affirmed the EU's commitment to ethical conduct in studies conducted at home and abroad. The legislation specifically requires applicants to submit a statement of compliance to GCP. However, this mechanism has been criticised as insufficient and often difficult to evaluate.¹

In respect to ethics, 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.*"² However, evidence shows that little attention has been paid to clinical trial ethics in assessments for EU marketing authorisations.³

International cooperation in the regulation of clinical trials, their review and inspection and capacity building in this area (Chapter 3)

The working group lists the standard requirements of a system for regulators of clinical trials in developing countries. Its first requirement is that all clinical trials in third countries be authorised by the NRA and/or by the concerned Ethic Committee(s) (ECs) in the host country. This requirement does not take into account the variability in standards for regulatory authorities and ethics committees. To accommodate this uncertainty one common standard should be adopted and applied to all clinical trials undertaken in third countries.

Ethics committee and NRA oversight (Chapter 4.1)

Research may only be undertaken if the research project has been approved by an Ethics Committee in accordance with Directive 2001/20/EC.⁴ The report cites the Declaration of Helsinki (Paragraph 15): "The ethics committee must have *the right* to monitor ongoing studies". HAI Europe encourages the EMA to go beyond the Helsinki Declaration and commit to actively monitor ongoing studies.

The working group report finds that it is the responsibility of the sponsor to ensure that an appropriate ethics committee reviews the clinical trial protocol. However, HAI Europe cautions that the sponsor can have a conflict of interest, between on the one hand to expedite a study through the rapid recruitment of participants and on the other hand responsibilities to undertake a thorough ethical review that may take additional time to complete.

The report goes on to suggest that if the NRA or Ethics Committees framework has limited oversight of the clinical trial in the third country, then the sponsor 'should' put in place alternative solutions in order to ensure adequate review of the clinical trial protocol. Furthermore, it is stated that an ethics committee should be able to withhold approval of a research proposal and upon its findings it 'should' be possible to suspend or prohibit the trial.

¹ 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

² Point 8 of the Introduction to the Annex of the Clinical Trials Directive 2001/83/EC.

³ *Ibid.* SOMO

⁴ Art. 6(2) and Art 9 of the Directive 2001/20/ECC, Art 9 and 10 Additional Protocol on biomedical research(COE), Paragraph 15 of Declaration of Helsinki, WHO (CIOMS) guidelines 2.

The word ‘should’ creates vague mandates that lack clear and unambiguous obligations and should be replaced with a clear instruction.

The report suggests that if an Ethics Committee does not exist, then it should be established as a pre-requisite for the clinical trial to take place. There should be clear guidelines for the establishment of an ad-hoc committee that avoids haste and conflicts of interest. Criteria should be adopted to ensure that an ethics review is not undertaken by a for-profit committee.

The working group recommends that the composition of the Ethics Committee be of multidisciplinary and independent representatives who can provide a complete and adequate review of the research proposals. According to the report, when illiterate persons form the focus of a study they ‘should’ also be considered for consultation in the Ethics Committee decision process. Moreover, the report continues that the Ethics Committee in the country where the trial is to be conducted ‘should’ have, as either members or consultants, persons with understanding of the community’s customs and traditions. Given the importance of the social and the cultural background of participants in medical studies, HAI Europe urges the EMA to make a stronger commitment to diversity in the ethics committee. Again, ‘should’ implies that these standards are aspirations whereas this provision needs to be a requirement of the Ethics Committees.

Fair compensation (Chapter 4.4)

Regarding compensation for persons who have suffered adverse side effects as a result of clinical trials, HAI Europe queries how compensation arising out of unwanted harm will be measured? Will compensation be relative to that for someone living within the EU or that for someone living in the country where the trial took place? If the latter be the case, then HAI Europe would be concerned that participants may not receive adequate compensation for any harm that they have suffered.

Vulnerable populations (Chapter 4.5)

When addressing vulnerable population and their risk of exploitation in clinical trials in third countries, the importance of considering and mentioning women specifically. This is especially true in countries where women are not accorded full rights either in law or in practice.

Placebo and active comparator (Chapter 4.6)

The EMA states that the capacity of a trial to produce reliable results is a prerequisite for the ethical justification of that trial. This chapter should consider and reference surrogate outcomes⁵, which may correlate with a real clinical endpoint, but does not necessarily, have a guaranteed relationship. Surrogate end-points should only be allowed where it has been clearly established that changes in surrogate outcomes predict changes in hard clinical outcomes (i.e. a reduction in morbidity and mortality).

Access to treatment post trial (Chapter 4.7)

⁵ Turner defines a surrogate outcome in a clinical trial as: “a laboratory measurement or a physical sign used as a substitute for a clinical meaningful endpoint that measures directly how a patient feels, functions or survives. Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint.” Temple R, ‘A Regulatory Authority’s opinion about surrogate endpoints- Clinical Measurement on Drug Evaluation edited by Nimmo WS (New York, Wiley, 1995).

Greater reflection is needed to ensure that the commitments made to access to treatment after a clinical trial is completed uphold the highest ethical standards. Despite the title of this chapter, the text states that sponsors cannot be expected to provide treatment to substitute the shortcomings of national health care systems, nor. Moreover, sponsors should not evade their post trial commitments simply by stating before the trial begins that they will not be providing any post-trial treatment.

The main motivation for companies to move clinical trials outside of the EU to developing countries is that they are less expensive to run in low and middle income countries. However, in these circumstances fewer healthcare options exist in developing countries for participants once the trial is finished than for participants in the EU. It is unacceptable for sponsors to neglect the ongoing medical needs of study participants. Sponsors that engage participants in the developing countries reduce the costs of clinical studies and specifically seek treatment naïve patients, must be responsible for ensuring participants' access to treatment after the trial is concluded.

The working group states that: “The cessation of a beneficial possibly life-saving or prolonging treatment at or after marketing of the product due to economic reasons (e.g. low personal income) of the patients and/or no reimbursement is problematic.” Whilst HAI applauds the recognition of this problem, a clear solution needs to be proposed.

Determine the practical steps to be undertaken during the provision of the guidance in the drug development phase (Chapter 5)

HAI Europe emphasises the need to undertake clinical trials that are appropriate to the disease burden in the developing countries. For example, a trial investigating a new medicine for baldness should not be done in a developing country as baldness is not a priority health need in that population. These guidelines should require that trials be relevant to the health needs in the countries where they are being carried out.