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Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted in third countries and submitted in marketing authorisation applications to the EMA

A Response

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1. I am a member of a United Kingdom NHS Research Ethics Committee and a retired Barrister. I am a member of the EFGCP Ethics Working Party. This is a brief response made within the limited timeframe set by the EFGCP. It is intended to serve as a pointer for further action rather than as a detailed examination of the issues raised in the reflection paper.

2. The practice of 'Clinical Trials Dumping' throws up issues of ethics and safety that must be addressed as a priority. I endorse the recommendation of the 2007 EMEA London Conference that the provisions of the 2001 and 2005 Directives must be evaluated and consolidated so as to provide better protection for research subjects of clinical trials in third countries. I make four general observations at the outset before dealing with issues of a more specific nature.

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3. Care must be taken to ensure that regulatory measures concerning research in third countries that govern applications for the Marketing Authorisation of new drugs within the European Economic Area are not misapplied in the interests of a tacit 'Pharmaceutical Protectionism'. By this, I mean a situation whereby applications in respect of new drugs trialled in third countries, and which are perceived as rivals for a domestic market share, are treated less favourably for that reason than equivalent studies conducted entirely within Europe. The proliferation of safe and cheap drugs to a wider population is an ethical objective in itself, no matter where it happens. So good rules must not be applied to a bad purpose, or to a collateral purpose that is political or financial, rather than ethical and scientific. Decisions on marketing authorisation must therefore be transparent and be capable of review. If the regulatory mechanism is not transparent, then legal challenges may be made to it.

4. We must be careful not to lose sight of the fact that clinical trials in Developing Countries have an important place in the furtherance of the public health of their indigenous populations and in the personal healthcare of research participants who might not have access to such medical treatments by other means. These trials might also confer public health benefits upon European member states with substantial immigrant populations from these host countries. Furthermore, improved healthcare outcomes in Developing World countries, with better access to treatments, could have subtle but beneficial economic consequences for Northern Hemisphere economies seeking new and expanding export markets in the aftermath of the recent (and continuing) global economic crisis, and especially in the export of medical and scientific expertise.

5. A balance needs therefore to be struck between regulatory safeguards that are shown to be necessary to protect the foreign research subject and the European consumer, by maintaining ethical standards alongside relevant scientific data quality, and the urge to impose an essentially Northern European ethical value system, embodied by the Helsinki Declaration, upon heterogeneous peoples on distant continents. These peoples might, and sometimes do, place different emphases upon the importance of informed consent and individual choice, or the role of the clinician, when measured against their own local health priorities for new treatments. A different approach to these ethical issues would not necessarily be perceived by local subjects as an ethical abuse. The mechanism for the regulation of third country research, whether in the context of an

application for EU Marketing Authorisation or otherwise, should therefore not become a vehicle for an uncritical or unreflexive form of 'Ethical Imperialism'.

6. A question that lies at the root of the reflection paper is the degree to which accepted values for ethics in medicine can be treated as universally applicable irrespective of their social and cultural context. I am not sure that that question admits of any clear answer. But I incline to the view that history has shown ethical values to be more relative than they are absolute. A second question following from the first is what is meant by 'ethical equivalence' in the context of the marketing authorisation of drugs based on foreign clinical data. The 2001 and 2005 Directives are the legal basis on which the test of ethical equivalence is to be founded. So what latitude can ethics committees and licensing authorities afford to local custom and local clinical practice in deciding that a study comes within or falls outside the ethical standards set out in, or referenced by, the 2001 and 2005 Directives? How should consistency and proportionality in their decision making be maintained given that health needs and priorities for researched communities will differ from region to region? These general observations assume a particular relevance in the light of the issues that are discussed below.

7. The timing of this reflection paper is significant. It follows the rule change by the U.S. Food and Drugs Administration (FDA), effective from 27th October 2008[1], such that applications for marketing approval for drugs or biologics based on data from foreign clinical studies, that were not themselves conducted under an Federal Investigational New Drug Application, will in future be required to demonstrate compliance with Good Clinical Practice as defined under the relevant Federal regulation[2], and not by the wider precepts of the Declaration of Helsinki. This has particular relevance to the acceptable use of placebo in preference to active treatment. It is also relevant to the question of whether the research participant in a control or comparative study arm should be given access to the best current prophylactic, diagnostic or therapeutic method of treatment as a basic ethical requirement of the study.

8. Critics of the FDA amendment have pointed to a possible relaxation in other ethical standards relating to publication requirements, conflict of interest, and the availability of drugs to subjects and communities after the termination of the study[3]. The FDA contests the risk of adverse consequences arising from the rule

[1] http://www.regulations.gov/search/Regs/home.html#documentDetail?R=0900006480537f08
[2] Code of Federal Regulations Title 21 Part 312, Section 312.120
[3] http://globalbioethics.blogspot.com/; entry for 8th May 2008

change. The FDA is specific, however, in asserting that the U.S. Government supports the underlying tenets of the Declaration of Helsinki, but that it is no longer appropriate for the relevant Federal legislation to require compliance with the Declaration in any of its present, previous or future forms[4].The FDA considers that the Declaration runs counter to Federal law and U.S. policy in certain key respects, and specifically on the matter of the use of placebo-controlled trials.

9. Earlier commentary from the EMA in June 2001[5] suggests that there are circumstances in which the use of a placebo-controlled trial will be justifiable in preference to the use of alternative standard treatment, for example where the public interest is served by increasing the number of treatments of similar efficacy and this cannot be demonstrated readily by recourse to a superiority study. The most recent revision to the Declaration of Helsinki in 2008 also contains a clarifying statement on the use of placebo controlled trials that was not present in the 2000 Revision. This latest version now crucially enables the use of placebo in trials of drugs for more than minor conditions, provided that compelling and sound methodological reasons can be made out and that the subject is not at risk of serious or irreversible harm[6]. This latest amendment has obvious relevance to the decision taken by the FDA and both appear to have been published in the same month. The EMA and FDA have since embarked upon a joint harmonisation initiative that includes a GCP inspection pilot that could embrace third country research[7].

10. The European Medicines Agency should therefore revisit the FDA rule change and decide whether it is necessary to issue a clarifying statement about it. The point now is to map the areas of divergence and similarity between the International Conference on Harmonisation guidelines on Good Clinical Practice (ICH GCP) and the 2008 Version of the Helsinki Declaration. This mapping exercise should focus especially, but not exclusively, on the question of placebo controlled trials. GCP, as interpreted under US Federal Law, should then be compared with the statement on Good Clinical Practice issued by the International Conference on Harmonisation in Guideline E6 (R1), in order to determine the points of variance or the degree of latitude in interpretation that is afforded by the one to the other. This is necessary because the FDA has stated

[4] Federal Register, April 28, 2008 (Volume 73, Number 82) [Rules and Regulations] page 22805, in the FDA response to Comment 10.
[5] *EMEA/CPMP Position Statement on the Use of Placebo in Clinical Trials with regard to the Revised Declaration of Helsinki*, London 28th June 2001, EMEA/17424/01
[6] Paragraph 32 of the 2008 Version
[7] http://www.ema.europa.eu/Inspections/docs/gcp/Q&A_on_FDA_EMEA_GCP_Initiative.pdf

that the GCP that will be applied is the GCP as incorporated and defined by the Federal legislation, and not Guideline E6, the latter being regarded as a stand-alone document that can be amended independently of the FDA. Comparison should then be made between the FDA interpretation of GCP and the 2008 Revision of the Helsinki Declaration so as to map the points of divergence and to issue further guidance upon them.

11. This exercise by EMA in the clarification of standards could present a timely benefit to the clinical research community in Europe and the United States, and particularly in the context of the marketing authorisation of drugs based on data from studies conducted in third countries. If there is variance between these various statements of ethical principle, then how might that affect applications for new drugs which seek simultaneous marketing authorisations in both Europe and the United States? How might it affect studies proceeding towards European Marketing Authorisation which depend heavily upon sponsors and researchers operating to U.S. compliance rules? Do the FDA rule change and the current EMA reflection paper mark a pivotal shift by European regulators to a different direction of travel from that of the U.S. Government with regard to the application of the Helsinki Declaration and ICH GCP, or not? What ethical concerns surrounding the FDA rule change remain in the light of the 2008 Revision to the Helsinki Declaration? Liaison with the FDA and with any working party of the World Medical Association on placebo controlled trials will be necessary.

12. The EMA and other consultative bodies should consider whether it is also necessary to issue additional guidance to clarify interpretative difficulties remaining after, or even arising from, the 2008 Revision of the Helsinki Declaration itself. This is especially necessary if doubt of ambiguity as to its terms might affect the success of a later application for marketing authorisation. Some issues requiring clarification are set out below.

13. One critic of the FDA rule change has indicated that a key divergence between ICH GCP and the Helsinki Declaration is the latter's requirement for the post-study availability of the tested drug to the study participants or their communities[8]. Another commentator on the latest revisions of the Helsinki Declaration has indicated that it is hard to tell whether the 2008 Revision now offers greater or lesser protection to the subject on the matter of post-study access to treatments[9].

[8] http://globalbioethics.blogspot.com/; entry for 8th May 2008
[9] Ruth Macklin. *The Declaration of Helsinki:another revision.* Indian Journal of Medical Ethics 2009 Jan-Mar; 6(1)

The 2000 Revision states in paragraph 30 that "*at the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study*". The 2008 Revision states at paragraph 33 that "*at the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits*". The later reworking seems to permit of a situation in which the sponsor might decide to provide something less than the superior treatment identified by the study and opt instead to provide some cheaper, but ethically more questionable, alternative. This provision is open to abuse. The EMA and FDA should specifically on this peculiarity and give guidance.

14. Questions about post-study access to treatment engage other ethical dilemmas that are intimately associated with the iterative history of the Helsinki Declaration. The first is that any improvement in local healthcare treatments in Developing World countries is better than none at all, and that providing less than the best available Western treatments to a study population, but more than the local standard treatment, is an ethical gain in itself. A second is that when the Declaration speaks of '*best current treatments*' as the comparative for third country research, is this to be interpreted as the '*best global*' or '*best local*' current treatment? And if it is '*local*', then how '*local*' must it be? Sponsors, researchers and research ethics committees need to know how determinant and prescriptive this matter of provision of post-study treatment must be to the success of an application for Marketing Authorisation, and what permissible forms such provision can take. The EMA should provide further clarification upon these matters. The FDA should also be invited to comment. If no further clarification can be given, because there is no ethical, clinical or operational consensus, then at least the public recognition of that fact will be useful.

15. Another point of disparity between U.S. Federal rules and the Helsinki Declaration is in the matter of compulsory registration of clinical trials. The Declaration extends the requirement to all clinical trials[10]. The U.S. Federal registration requirements do not extend to Phase I studies of drugs or biologics, or small feasibility studies of medical devices[11]. What steps will the EMA and FDA take to ensure that registration requirements are harmonised? Should these

[10] at Paragraph 19 of the Declaration.
[11] http://clinicaltrials.gov/ct2/info/results

Federal exemptions be abolished in favour of the same terms of inclusion as found in the EudraCT scheme?

16. Another matter of importance is the establishment of a clinical database that will enable data from third countries to be searched to address questions of ethnic sensitivity in therapeutic applications. The lack of availability of facilities for Bioequivalence studies has been cited as a major obstacle to the proliferation of locally manufactured generic treatments for certain major diseases in East Africa[12]. Could this be a solution? Data from the Complete Clinical Data Package[13] used for registration purposes would feed into this database. This would have the ethical objective of reducing the duplication of clinical trials in third countries by providing a commonly accessible source of data that could be used for Bioequivalence and other studies. A technical objective would be to configure that database for meta-analysis, if this is possible to achieve. Technical experts should comment on this proposal.

17. The importance of the research ethics committee and local ethics review board has been discussed in the reflection paper. Arguably, by one reading of the FDA rule change, the activities of the independent ethics committee might now assume a greater centrality than was hitherto the case. As the paper remarks, there is a need for greater cooperation between European and non-European ethics committees in facilitating shared standards. But there is also a need for greater cooperation between them in information exchange with reference to ongoing clinical trials. One problem that has not been resolved within the reflection paper is the organisational and decisional problems of a clinical trial that involves simultaneous research activity upon human research participants within a European member state but also in a foreign country. Other commentators have elsewhere suggested improving and formalising the use of the Voluntary Harmonisation Procedure [VHP] to enable an expedited clinical trial authorisation to be given to a clinical trial taking place within several European member states. Responses to the recent consultation on the European Clinical Trials Directive have tentatively suggested that the VHP procedure might also be extended to the process of ethical review[14]. But as yet there is no consensus as

[12] *Study on the Feasibility of Conducting Bioequivalence Studies in East Africa,* 2009, published by GTZ

[13] ICH Tripartite Guideline *Ethnic Factors in the Acceptability of Foreign Clinical Data E5 (R1) Step 4 Version dated 5th February 1998*

[14] The question is raised in the ECRIN/RMICRE Multidisciplinary Workshop on Research Ethics Committees and Ethical Review in Europe, 19th January 2010, Barcelona;

to how ethical review might be expedited in the context of a multinational European clinical trial and therefore even less of a consensus as between European and non-European governance bodies.

18. It follows that consideration should be given to the distinct question of how European research ethics committees are to deal with their foreign counterparts in providing ethical review to a multinational clinical trial that is to be conducted simultaneously in European and non-European countries. This question also has relevance to other types of research, such as observational studies involving human tissue that might be analysed within Europe but sourced from elsewhere. The point at issue is the permissible scope of the ethical review to be carried out by the European research ethics committee, when measured against that of its non-European counterpart. How much of an overlap should there be between the function of the one when measured against the other? Should there be an overlap at all?

19. The 2001 Edition of the United Kingdom Governance Arrangements for Research Ethics Committees requires committees to consider the impact of the research protocol on the community, in terms of capacity building and how such improvements will be implemented. Such ethical considerations are very relevant to the conduct of research studies in the Developing World. However, it is the general tenor of the Standard Operating Procedures for UK Research Ethics Committees [RECs] that it is not their responsibility to review research conducted outside the United Kingdom. The same instruction is applied in a general way to research conducted outside the United Kingdom that is supportive of research taking place within it[15]. The guidelines state that it is more appropriate that these research activities are subject to ethical review in the country where the research takes place, by taking account of local differences in law, ethics, culture and the consent process. This statement overlooks the fact that a drug product proceeding towards European marketing authorisation requires an investigation of the ethical standards of the research no matter where the research is conducted. So it is short-sighted to assume that a domestic research ethics committee can never find itself in a situation in which it is necessary or desirable to examine the ethics of research conducted abroad. How can a domestic research ethics committee properly approve a protocol knowing that it contained

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http://www.ebmt.org/2relatedmeetings/EFGCP/Agenda%20Ethics%20Committees%20Workshop_19Jan2010.pdf

[15] Standard Operating Procedures for UK RECs Version 4.1, paragraph 11.38

ethical abuses that were specifically earmarked for perpetration offshore? The whole of the study could thereby be held to be tainted by the part. Increasing cooperation between national competent authorities means increased cooperation between ethical review bodies and the organisational means to bring this about. A specific problem in this regard is that there is no formal mechanism within the UK research governance framework whereby information can be shared between domestic and foreign research ethics committees in order to arrive at a common decision in the ethical review of a trans-national research project.

20. Decisions relating to the grant of Marketing Authorisation in the EEA will necessitate a consideration of matters of scientific quality and safety that might not have been considered in the course of the preliminary ethical review, especially where such matters arise in the course of the study and not at the outset. As such, it is clear that the resolution of the marketing application will depend chiefly upon decision of the licensing authority and not that of the research ethics committee. Nevertheless, the content of the European Public Assessment Report will contain an examination of the ethical equivalence of the study in the manner in which foreign data was gathered and used. It is possible that this examination might be more usefully and speedily carried out if there were to be some protocol in place to assist the transfer of information between European and non-European research ethics committees at the ethical review stage for research studies taking place in both European and non-European member states.

21. The question of how to provide effective governance for third country research allows for some challenging opportunities for competent authorities and research ethics committees. Future applications for marketing authorisations could be linked more closely to the assurance that sponsors would provide capacity building in local communities in which the drug had been tested and an enhanced regime of post-marketing audit and inspection might be used to examine whether this was in fact taking place. There would have to be consequences for non-compliance. This might also involve a fundamental shift in the way in which research ethics committees conduct their business. I commend the excellent article cited in the footnote[16] which explores the potential use of the 'partnership model' by members of research ethics committees, who would thereby facilitate a

[16] D.W.Dowdy. *Partnership as an ethical model for medical research in Developing Countries; the example of the Implementation Trial*.J.Med.Ethics 2006;32;357-360 and see articles cited therein.

more active and equal participation by local communities in the research process by 'brokering' community based research partnerships. Such a model would be appropriate where the local communities and researchers were equally matched in bargaining power so as to negotiate their own involvement in the research process. This novel governance approach might also be considered in the context of the 'Implementation Trial', as applied in Developing World countries, whereby research outcomes are more closely linked to local health priorities and are measured over time.

22. The time for further consultation that should follow this reflection paper is also a good opportunity to revisit the complex issue of how access to therapeutic drug treatments in the Developing World and in poorer European neighbour countries can be stimulated by initiatives in the field of Intellectual Property Law. The question has relevance to the best ways in which orphan drugs and treatments for 'Neglected Diseases' should undergo marketing authorisation. Put another way, should there be a grant of preferential terms for marketing authorisation of drugs marked for strategic applications in the Developing World, akin to the regulatory incentives recently introduced in the fields of paediatric medicines and advanced therapies? The problem, however, is that Developed World solutions do not necessarily apply to Developing World problems, and I am concerned that providing additional 'regulatory leverage' to the pharmaceutical industry could exacerbate the problem of drug supply in African and Asian countries rather than resolve it. There has been much published material on the topic of the reform of patent and copyright in research and I have not been afforded sufficient time to examine the issue in proper detail for the purposes of this response to the EFGCP. Suffice it to say that one key issue is whether stimulus for drug research to benefit communities in the Developing World should be provided from the top down, for example by legislative or other governmental reforms to thin the 'Patent Thicket', by further modification to the WTO TRIPS Agreement, or by making calls on Industry to reduce market costs. Alternatively, could further initiatives be taken from the bottom up by means of novel contractual solutions such as 'Creative Commons' agreements, by targeted public activism, or other means? Should a combination of these methods be adopted as the best recourse? There are two approaches that are reflected in this; the one to increase intellectual property ownership and the other to reduce it by what has become known as a 'copyleft' approach. These issues, and others like them, should be debated as

widely as possible and I invite the EMA, EFCGP and other agencies to facilitate this as a matter of importance.

Dated 4th July 2010 C.L. Roy-Toole