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24 October 2012

Vice-President Maroš Šefčovič
Acting European Commissioner for Health and Consumer Policy
European Commission
B-1049 Brussels
Belgium

Dear Mr Šefčovič,

European Commission Proposal for a Clinical Trials Regulation

We refer to the European Commission's Proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/209/EC (COM (2012/0192 [COD] dated 17 July 2012; related Press Release IP/12/795 and MEMO 12/566).

We previously participated in the public consultation on the functioning of the 2001 European Clinical Trial Directive (Directive 2001/20/EC; "EU CTD"). We agree that it is not serving its intended purpose, and that its repeal is highly appropriate. We have reviewed the proposed regulation and welcome many of its key improvements, such as a single submission point for EU clinical trial authorisation, more flexibility for consent in trials in emergency situations and measures which will decrease trial indemnity costs within the EU. The proposal's provision for less burdensome rules and shorter approval timelines for "low intervention" clinical trials is also appreciated since like most trialists, we strongly advocate a proportionate "risk-based" approach to trial regulation to facilitate processes for "low-risk" trials.

However, we do have significant remaining concerns, and feel it important to highlight these to you. Firstly, we feel that the definition of "low intervention" trials should be extended to trials testing established treatments with good safety profiles for novel uses that are not standard practice (e.g. aspirin for cancer prevention). Another reservation is that the regulation appears to be directed more towards measures to expedite study initiation (such as the approval process) rather than facilitation of overall trial conduct and oversight, and in so doing fails to address many of the other previously identified major problems with the EU CTD. In particular, there is still inappropriate emphasis on single adverse event case reporting for safety assessments and on inefficient approaches to trial conduct and monitoring that derive from the International Conference on Harmonisation Guideline for Good Clinical Practice ("ICH-GCP").

Although we recognise that ICH-GCP is well-intentioned, its interpretation and implementation in practice has focused on specific aspects of its wording rather than its overarching intended objectives. This has resulted in rigid procedures that have been unduly prescriptive and obstructive. By contrast, it is now widely agreed amongst most researchers and many regulators that monitoring should focus on procedures that truly determine quality and, as you will be aware, the EMA recently issued a proposal for risk-based quality management in clinical trials[1]. Similarly, many parties now acknowledge that the current system of reporting of "suspected unexpected serious adverse reactions" (SUSARs) on a case-by-case

[1] European Medicines Agency. Reflection paper on risk based quality management in clinical trials. 4 August 2011. EMA/INS/GCP/394194/2011

basis (rather than as grouped reports with a meaningful denominator) involves substantial expenditure of money and effort, but rarely leads to useful insights or improved safety. A more effective strategy for safety monitoring in trials would instead employ a risk-based approach with regular review by independent Data Monitoring Committees of the emerging safety data unblinded to the study treatment allocation and considered in the context of the efficacy results. The cogency of these concerns has been recognised by the FDA, which has issued revised guidance and an amendment to its safety reporting requirements[2], but the proposed EU regulation's safety reporting requirements remain largely unchanged despite this being raised as an area of concern in the public consultation.

Whilst Directive 2001/20/EC does not make specific reference to ICH-GCP (although Commission Directive 2005/28/EC of 8 April 2005 ["the GCP Directive"] does state that the ICH 1995 consensus paper on GCP should be taken into account), we note that Article 44 of Chapter VIII of the proposed regulation relating to trial compliance with the protocol and good clinical practice reinforces the dependence on ICH-GCP further by stating that:
"..the sponsor and the investigator, when drawing up the protocol and when applying this Regulation and the protocol, shall take due account of the quality standards set by the detailed international guidelines on good clinical practice of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)."
Therefore, although we applaud the proposed regulation in allowing the sponsor provision to determine the extent and nature of monitoring based on the clinical trial characteristics, if the regulation persists in referencing ICH-GCP as the quality standard then successful delivery of a risk-based approach is unlikely to be achieved (unless there is a corresponding fundamental shift in focus from the details of ICH-GCP to its core principles, or indeed modification of ICH-GCP itself).

In summary, whilst we acknowledge that the EU Regulation offers the promise of a more facilitatory environment for trials, unless the above concerns are addressed, there is a risk that the current obstacles will become even more established. Ultimately, this could mean that the huge potential of clinical trials for assessing the safety and efficacy of new and existing treatments and, thereby, for producing improvements in health care and public health in Europe and beyond will not be fulfilled.

We would therefore be grateful if you could take our points into consideration and would appreciate your feedback on whether further changes to the proposed regulation will be possible.

Yours sincerely,

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University of Oxford

cc: Dame Sally Davies (Department of Health)
Sir Michael Rawlins (National Institute for Health & Clinical Excellence)
Sir Kent Woods (Medicines and Healthcare products Regulatory Agency)
Sir John Bell (Government Life Sciences Champion)
Sir Mark Walport (Wellcome Trust)
Sir John Savill (Medical Research Council)

[2] US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Draft Guidance for Industry and Investigators. Safety Reporting Requirements for INDs and BA/BE Studies. September 2010.