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**Academic and charitable sector position on the possibility of
ICH-GCP becoming a legal requirement in the Clinical Trials Regulation
October 2013**

Key points

- Mandating the full requirements of ICH-GCP in the Clinical Trials Regulation should be opposed
- ICH-GCP guidelines do not allow room for proportionality which is problematic for academic trials and undermines the intention of the Regulation to create greater scope for risk-adaptation.
- Mandating ICH-GCP would create significant and disproportionate costs in running many academic trials with no corresponding patient benefit.

We are concerned about proposals to make International Conference on Harmonisation Good Clinical Practice guidelines (ICH-GCP) a legal requirement in the Clinical Trials Regulation. We believe that such a move would remove the proportionality achieved in the current draft of the Regulation, to the detriment of non-commercial clinical research in Europe. Mandating ICH-GCP in legislation would not improve patient safety beyond that in the current provisions within the proposed Clinical Trials Regulation. The implementation of ICH-GCP would mean that the same strict and inflexible rules would be applied to all trials, preventing the use of simple, practical approaches where these would be appropriate and effective.

Research indicates that the inappropriate application of ICH-GCP for academic studies could increase costs as much as ten times compared to taking a risk-adapted approach.¹ For example, a case study below demonstrates that applying ICH-GCP site monitoring standards would require significant extra resources compared to taking a risk adapted approach. Even for that simple trial, ICH-GCP monitoring required 2100 days of staff time—equivalent to 10 people employed for a year – to accommodate site monitoring visits. We believe mandating ICH-GCP would create significant and disproportionate costs in running many academic trials with no corresponding patient benefit. Such an approach would also reduce the number of trials which could be funded by non-commercial bodies.

Background to ICH-GCP

Clinical trials of investigational medicinal products must be undertaken in accordance with an appropriate standard of Good Clinical Practice. ICH-GCP guidelines were developed in 1996 by the pharmaceutical industry and regulators to facilitate multinational trials. The guidelines detail specific procedures and reporting that must be followed by clinicians and staff when undertaking clinical trials. While ICH-GCP is generally thought to provide a useful standard for commercial studies, it is less relevant, and often difficult to apply, to trials in non-commercial settings.

Concerns with making ICH-GCP a legal requirement in the Regulation

Mandating ICH-GCP standards would undermine the risk proportionality introduced in the Commission's draft of the Clinical Trials Regulation. Particular issues include that:

- The ICH-GCP guidelines were written by industry and regulators with no input from the academic community and are based on requirements for commercial trials intended to generate data for

¹ Eisenstein et al, Sensible approaches for reducing clinical trial costs, Clinical Trials, 2008
<http://ctj.sagepub.com/content/5/1/75>



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marketing authorisation for drugs. Many academic trials are designed to improve our knowledge of a drug, not to inform regulatory submissions and therefore the same processes will not always be relevant.

- The ICH-GCP guidelines do not allow room for proportionality which is problematic for academic trials and undermines the intention of the Regulation to create greater scope for risk-adaptation. For example, for low-intervention trials based on standard care, the requirements of ICH-GCP may greatly exceed the usual standards applied in routine care. This disproportionate burden will make it much more difficult and costly to run simple trials.
- There is general consensus on the principles from which ICH-GCP are derived and these key elements are already included in the draft Regulation. However, if additional elements of ICH-GCP are included as a legal requirement, regulators would have no scope for interpretation or flexibility on the procedures required to implement these principles. All trialists would be required to follow set processes that may not be the most effective way to conduct clinical research. This would prevent the use of simple, practical approaches.
- It is unlikely that all sites that currently conduct clinical trials would be able to meet the exacting process requirements of ICH-GCP. Mandating these requirements may therefore make some sites ineligible for clinical trials of investigational medicinal products.

Recommendation

We call on the members of the Council to oppose mandating the full requirements of ICH-GCP in the Clinical Trials Regulation. Members of Council should support the Commission's original drafting of Article 44 that states that "due account should be given" to the ICH guidelines. However, we consider that there would also be benefit in amending Recital 29 to ensure consistency with Article 44 and to avoid legal uncertainty (see below).

Suggested Amendment to Recital 29

The members of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) have agreed on a detailed set of guidelines for good clinical practice which are now an internationally accepted standard for designing, conducting, recording and reporting clinical trials, consistent with principles that have their origin in the World Medical Association's Declaration of Helsinki. When designing, conducting, recording and reporting clinical trials, detailed questions may arise as to the appropriate quality standard. **In such a case, due account should be taken of the quality standards set by the ICH guidelines on good clinical practice ~~should be used as guidance for the application of the rules set out in this Regulation~~**, provided that there is no other specific guidance issued by the Commission and that those guidelines are without prejudice to this Regulation.

Case studies demonstrating the difficulties of making ICH-GCP a legal requirement

Use of fibrinogen in a clinical trial

Clinical stocks of fibrinogen are routinely stored at room temperature, which is sufficient to ensure patient safety given the stability of the drug. However, under ICH-GCP the fibrinogen used in a trial would have to be held in a separate cupboard, with the temperature monitored and documented, in order to fulfil GCP requirements. These requirements, which go beyond that of standard clinical care, create additional administrative work for those involved in the study and logistical issues in assigning an exclusive area to store the drug, despite the fact that these requirements do not improve patient safety.



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Inspection requirements under ICH-GCP

MDP 301 was a large international placebo-controlled RCT international HIV prevention trial. It enrolled 9385 women (healthy volunteers). Each woman was followed up for a year. The women were recruited from a total of 10 sites in 4 different countries.

The study was undertaken by UK's Medical Research Council with a view to submission of the data for licensing and therefore adhered closely to the principles of ICH-GCP. Following the study a review was undertaken to determine if proportionate forms of monitoring could have reduced the amount of resources used to support the trial compared to the ICH-GCP standards that were followed.²

There were a total of 210 site monitoring visits over the course of the study; the visit length and number of monitors varied, but it was estimated that on average each visit required the resources of 10 person-days each. Therefore the site monitoring of the study took an estimated **2100 person-days**. This would be equivalent to about 10 people employed for a year to focus solely on accommodating site visits for a single trial.

This was a simple study in healthy people, so the case notes were short and there were few events to review. Monitoring a trial in a sick population would require far more time and resource because of the complexity of the medical records and clinical details.

The MRC concluded that most of the more serious monitoring findings could have been identified without site visits by a central monitoring committee, thus potentially reducing the number and length of the visits and allowing better targeting of sites in most need of support. However, mandating ICH-GCP requirements in legislation would mean that all trials would be subject to this high level of monitoring and associated cost and time burden, even when this is disproportionate to the risks.

Novel trial strategies: postal recruitment to research

Novel trial strategies such as mail-based postal studies can be highly cost-effective and facilitate studies which are of vital public health importance. For example, aspirin is commonly prescribed as primary prevention for cardio-vascular events for diabetic patients without vascular disease, despite a lack of reliable knowledge of the risks or benefits of this approach. The ASCEND trial has been designed to address this importance evidence gap.

By using simple mailed questionnaires in place of much more costly face-to-face patient visits (which require clinic space and staff resource), the study has been able to successfully recruit 15,000 participants in a very cost-effective manner, thus making maximum use of limited resources. However, mandating ICH-GCP would mean that it would not be possible to use such innovative and cost effective designs, due to requirements around informed consent and for face to face interviews

² Bakobaki et al, The potential for central monitoring techniques to replace on-site monitoring: findings from an international multi-centre clinical trial, Clinical Trials 2012 <http://ctj.sagepub.com/content/9/2/257>



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Eligibility assessment of potential participants

THRIVE and REVEAL are cardiovascular outcome trials involving over 25,000 and 30,000 patients respectively. These trials were carefully designed so that potential participants were identified from their electronic medical records and invited to attend a screening appointment with a specially-trained nurse (under the oversight of a local medically-qualified investigator). Patient eligibility was assessed using a bespoke electronic case report form system which included biochemical assessments of liver, renal and muscle disease. Potential participants could only enter the trial if they satisfied the inclusion criteria and did not fulfil any exclusion criteria.

ICH-GCP requires closer involvement of a medically-qualified person, therefore this approach to recruitment could not have been used if ICH-GCP was a legal requirement. However, in this example closer medical supervision at recruitment would not have affected the safety of participants or quality of the trial data.

Organisations

Cancer Research UK

Cancer Research UK is the world's largest cancer research charity. Last year we spent over 387million EUR on research. We fund over 240 studies in the UK and in total over the past ten years we've supported or endorsed 323 trials. We recruited 37,000 people on to trials last year. Our investment means that 16.8 per cent of cancer patients in the UK now participate in research.

The Academy of Medical Sciences

The Academy of Medical Sciences promotes advances in medical science and campaigns to ensure these are converted into healthcare benefits for society. Our Fellows are the UK's leading medical scientists from hospitals and general practice, academia, industry and the public service. The Academy seeks to play a pivotal role in determining the future of medical science in the UK, and the benefits that society will enjoy in years to come. We champion the UK's strengths in medical science, promote careers and capacity building, encourage the implementation of new ideas and solutions – often through novel partnerships – and help to remove barriers to progress.

Medical Research Council

The Medical Research Council is a publicly-funded organisation dedicated to improving human health.

We support research across the entire spectrum of medical sciences, in universities and hospitals, in our own units, centres and institutes in the UK, and in our units in Africa.

Wellcome Trust

We are a global charitable foundation dedicated to achieving extraordinary improvements in human and animal health. We support the brightest minds in biomedical research and the medical humanities. Our breadth of support includes public engagement, education and the application of research to improve health. We are independent of both political and commercial interests.

For more information please contact Daniel Bridge daniel.bridge@cancer.org.uk/+44 (0)203 469 8153