



Direct Line: 020 7670 4727
Direct Fax: 020 7670 4815
E-mail: j.darbyshire@ctu.mrc.ac.uk

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Ms Birka Lehmann
Directorate General Enterprise
European Commission
1049 Brussels
Belgium

BY E-MAIL & HARD COPY

Dear Birka

EU Commission Directive on Good Clinical Practice

I am writing to you on behalf of the Steering Group of the Joint Project to Codify Good Practice in Publicly-Funded Clinical Trials, established by the Medical Research Council and the Department of Health in June 2003 which I chair.

We are grateful to have this opportunity to respond to the Commission consultation on the Draft Directive on GCP. As you know, non-commercial organisations committed to high quality clinical trials, such as the Medical Research Council, the Department of Health and National Health Service, and research charities such as Cancer Research UK, have been concerned that "academic" trialists have had little access to the processes by which important regulations that affect their ability to conduct trials have been decided. They and their European counterparts have a wealth of expertise in managing clinical trials to the highest of standards for the benefit of patients of today and tomorrow. We are therefore delighted that the Commission has been listening to this community and hope that this will continue.

As you know, the project teams have worked closely with academic trialists and trial managers to clarify and assist the implementation of the requirements of the EU Directive, and more specifically the United Kingdom regulations. We have also worked in partnership with the UK Medicines & Healthcare products Regulatory Agency, both to help academic trialists understand and fulfil the regulatory requirements without jeopardising the future for such trials. We have worked with the European Science Foundation in considering the needs of European trialists, and hope to further that collaboration specifically to facilitate pan European trials.

Principles

A principle fundamental to the work of the Joint Project is that the approach to satisfying the principles of ICH GCP should be appropriate and proportionate to the risks of the individual trial, and the additional "red tape" should be minimal. This means the regulations need to accommodate quality and risk management procedures and organisational models that may differ from those typical of the pharmaceutical industry. Otherwise, the regulations may become a burden and a disincentive to trials that Europe needs for the health and well being of its citizens and of a type that the pharmaceutical and biosciences industries do not do.

Consequently, we welcome the recognition in the Draft GCP Directive that the Commission and Member States should use the full flexibility allowed by the EU Clinical Trials Directive (and now the GCP Directive) so that high quality, non-commercial trials flourish within the EU for the benefit of patients and the wider public.

We are concerned that the Commission Directive on GCP, which will be legally binding, goes beyond the principles of GCP under Article 1(3) of the EU Clinical Trials Directive by also including detailed guidelines (Articles 4, 6, 7 & 8). The detailed guidelines should be dealt with through the prescribed procedures such that they can be adopted, if approved, as non-binding guidance.

Preamble

"(11) Non-commercial clinical trials conducted by researchers without the participation of the pharmaceutical industry may be of great benefit to the patients concerned." We welcome this statement. In practice, many companies collaborate with university and hospital sponsored trials that are funded by non-commercial organisations by donating the drug(s) *without* imposing conditions on the control of the trial. We suggest the Commission's point would be clearer if stated as follows, "Non-commercial trials, sponsored by organisations other than industry, may be of great benefit to the patients concerned, not least when they address important public health questions that are not of commercial interest."

"(11) ... it could be necessary,... that Member States foresee specific modalities ... be applied to these [non-commercial] trials not only when conducted with authorised medicinal products and on patients with the same characteristics in order to comply with the principles imposed by this Directive" in relation to manufacturing, import, documentation and archiving. This statement is welcome.

"(11) application of certain principles of good clinical practice may be ... guaranteed by other means." In fact, we would not argue that "certain principles [might be] *unnecessary*," as we believe that the *principles* guaranteed by appropriate and proportionate application of good practice in academic trials.

We recommend that the Commission consider including a statement to the following effect. "In applying the principles of Good Clinical Practice, Member States should ensure that the regulatory requirements and procedures are appropriate to the purposes and kinds of clinical trial being regulated, and proportionate to the specific risks to be controlled to fulfil the Directive's requirements.

Chapters

Chapter 1 Good Clinical Practice...

We welcome "**Article 1 (3)**. *When applying these principles, detailed guidelines and requirements on non-commercial clinical trials... without the participation of industry, Member States may introduce specific modalities to take into account the specificity of these trials...*" However, we suggest the Commission consider the following.

- Either delete "without the participation of industry" or replace the text so as to exclude the possibility that donation of trial drug and/of contribution to the costs of the trial by a commercial organisation would count as "participation" that would exclude the trial from an appropriate and permitted degree of flexibility.

Chapter 3 Manufacturing or import authorisation

We welcome the flexibility suggested by **Article 9 (2)**, but suggest that it should retain the wording contained in the earlier draft, which provided for exemption for assembly in hospitals and health centres. The current wording could be interpreted as applying only to hospital pharmacies.

We are concerned that in broadening its scope to include “medicinal products,” the current wording in **Article 10 (1)** will be interpreted to mean that authorisation must specify individual products to be manufactured, rather than types or classes of product. This would increase the administrative burden without in any way adding to the safety of patients. We suggest that the Article’s purpose is well covered by referring only to “pharmaceutical forms.”

Chapter 4 Documentation constituting the Trial Master File and archiving

Currently, most non-commercial sponsors subject a trial to independent audit (**Article 16**) when the risk profile is similar to that of commercial trials, or because the existing controls indicate a “for cause” inspection. MRC’s experience is that independent clinical trial auditors are attuned to the requirements the detailed guidelines of the ICH and try to apply these to trials with a different risk profile, usually inappropriately. There is not currently a large enough body of independent auditors with experience of effective management of academic trials to make audit a routine requirement in practice even if to do so were considered to be necessary.

Chapter 6 Inspection Procedures

We ask the Commission to consider applying the provision made in **Article 1 (3)** (see above) also specifically to Chapter 6. It would be unfortunate were inspections to be conducted against a set of Member State requirements that were out of step with Article 1, which provides flexibility to adapt to the specific circumstances of non-commercial trials. Current inspectors are drawn almost exclusively from an industry background. Member States need to ensure that inspectors have the competencies to inspect against the full range of systems permitted by the flexibility intended in the Directives. They also need to be able to work to with multinational, collaborative trials. This may present some challenges, as individual members states have yet to implement the EU Clinical Trials Directive.

Transparency of the language

We have encouraged UK trialists to read the draft Directive and to share their responses with us. This submission incorporates the results of that consultation. Almost universally, trialists complained about the difficulty of the terms used in the Directive, such as “modalities,” and the ambiguities resulting from imperfect translation. We strongly encourage the Commission to ensure the final Directive is clearer, and suggest it be accompanied by a simple, “plain English” guide to the requirements. That could save a lot of unnecessary worry and comment.

In conclusion, we congratulate the Commission on taking a major step towards promoting a regulatory environment that supports high quality trials that European patients need.

Best wishes.

Yours sincerely

Janet H. Darbyshire OBE FRCP FFPHM
Director, MRC Clinical Trials Unit
Professor of Epidemiology