



Principles of Independence Governing Clinical Trials Undertaken by the Gynaecologic Cancer Intergroup

The GCIG has been in existence since 1994, and during the last 15 years has conducted many trials, some of which have changed the standard of care. The GCIG is uniquely placed to conduct international trials to a high standard, and has acquired a strong reputation for quality and expertise. Some of these trials have been resourced by public funding and wholly designed and run by researchers; so called non-industry trials. Others have been funded by industry, and in some cases, sponsored by industry. This paper sets out the background and a number of criteria, which require to be in evidence as a means of ensuring that GCIG studies are being conducted in a way that guarantees independence and can be seen to be so doing.

Any attempt to define principles governing GCIG activity needs to recognise that GCIG Groups currently number 23 and come from North and Central America, Europe, Australasia and Korea/Japan. These countries have their own rules regarding clinical trials, and the European Union has a legal framework, the European Clinical Trials Directive 2001/20/EC (and 2005/28/EC), which covers good clinical practice (GCP) in the conduct of clinical trials on medicinal products (and the manufacturing of medicinal products). Not only do these individual jurisdictions impose complexity in terms of international trials but the Groups themselves function in different ways, particularly with regards to funding. Some Groups are able to acquire public funding for clinical trials, others depend far more heavily on commercial funding, and some studies are supported by a mixture of public and commercial funds.

Furthermore, the conduct of large phase III clinical trials frequently requires multiple partnerships not only between cooperative clinical trials groups but also, government agencies, industry and patient advocacy groups. Indeed, this is fundamental to the

GCIG with the establishment of formal categories of membership including Industry Partners and National Agency partners. Thus the intersect between cooperative groups and industry partners is of mutual benefit but must be guided by clearly agreed upon principles.

It is possible to classify clinical trials as 'commercial' or 'non-industry' depending on reliance or otherwise on commercial funding, but these definitions are imprecise and are, anyway, viewed differently by different individuals. Rather than dwell on arcane definitions, the GCIG views the independence of investigators in the development, conduct, analysis and reporting of clinical trials as the crucial element.

The rationale for the GCIG to publish principles of independence is to provide transparency in assessing the GCIG trials. The need for this arises because of concern regarding problems with industry sponsored clinical trials (for example, Wynia & Boren, 2009). With increasing reliance on Industry for funding and access to new drugs, GCIG requires to be able to partner industry in clinical trials, but at the same time, be able to demonstrate that badged trials have been appropriately designed, conducted, analysed and reported.

The following seven principles cover trial development, peer review, sponsorship, conduct, data collection/database ownership, analysis and reporting.

1. Trial Development

GCIG trials must be developed or at least co-developed, by at least one GCIG Group. Any industry trial that is thought to have a flawed design which cannot be amended will not be considered eligible for GCIG badging. This will avoid pit falls such as inappropriate comparisons, endpoints either clinical or surrogate, and under powering.

2. Trial Peer Review

GCIG trials should have been adequately peer reviewed to guarantee the scientific validity of the study and the likelihood that it will be successfully completed. Such peer review could include comment from GCIG Groups but there should also be an independent Trial Steering Committee, which include independent membership, or equivalent to scrutinise the protocol and sign it off before the trial opens.

3. Sponsorship/Funding

If the trial is funded wholly by industry, it is preferable that the study sponsor is not Industry, but a University, national cooperative trials group or other suitable public body. In Europe the sponsor has a number of important legal responsibilities, which make commercially sponsored studies much more difficult to maintain investigators' independence. It is desirable to have a prior agreement that the Pharma involved makes the trial database available to the investigators.

4. Conduct/Control of the Trial

The trial should be led by a GCIG Group, which effectively controls the trial, run and conducts the analysis. When GCIG Groups collaborate, the data should be accessible to all Groups with the involvement of the lead Group. All collaborating Groups and co-investigators should understand and comply with Good Clinical Practice.

5. Data Management

The trial collection data can be organised by a clinical research organisation (CRO), but the CRO should not hold the database and should not be able to pass data directly to a commercial funder. For registrational trials, formal agreement with the industry partner can be developed in advance to allow access to appropriate elements of the database, e.g. safety data.

6. Trial Analysis

The trial should be analysed by the trials statistician and not by an Industry sponsor, and only when the data are sufficiently mature. However, the analysis can be undertaken with the Industry sponsor in co-operation. The analysis should be seen by the Data Monitoring Committee.

7. Reporting of the Trial

The trial should be reported independently of a funding industrial sponsor. The final draft could be shared with an industry sponsor but any proposed changes would need to be approved by the investigators. Authorship will be agreed by the collaborators at the outset but all authors should have access to trial data and the reporting author must be able to guarantee those data.

In situations where industry acts as the legal sponsor contracts should state clearly that trial analysis and reporting are the responsibility of the lead GCIG group.

In the situation where industry funds a non-industry sponsored trial, a contractual agreement may be drawn up between industry and the sponsor acting for the GCIG group to share the database after publication of the main analyses.

These principles are not intended to be aspirational, but should be in place for all trials under the GCIG banner, and would be available on the GCIG website.

Reference

Wynia M and Boren D. 2009. Better regulation of industry-sponsored clinical trials is long overdue. *Journal of Law, Medicine & Ethics*; **37(3)**: 410-9