



GCIg

PRINCIPLES OF INDEPENDENCE

v Sept 2017

Submitted to Exec.COMMITTEE Sept 2017

Submitted to Exec. BoD: October 2017

Approved: November 2, 2017

Principles of Independence Governing Clinical Trials

The foundation of this has been directly taken from the 2010 document and updated/revised.

The GCIg has been in existence since 1993 (founded), 1997 (formally), 2011 (incorporated), and during the last 24 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 a number of criteria, which are required as a means of ensuring that GCIg studies are being conducted in a way that guarantees independence and transparency. At the 2015 Strategic planning meeting, it was proposed that a prospective checklist be developed, and be used before trials are badged, to ensure the GCIg criteria are being adhered to.

Any attempt to define principles governing GCIg activity needs to recognise that GCIg Member Groups (currently twenty-eight) come from North America, Europe, Australia/New Zealand and Asia. These countries have their own rules and regulations regarding clinical trials [eg. the European Union has a legal framework, the European Clinical Trials Directive 2001/20.EC (and 2005/28/EC)] which cover 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 interaction 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 viewed differently by different individuals/groups. 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 the assessment of 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 needs to be able to partner with industry in clinical trials. At the same time, GCIG must 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 protocols must be developed or at least co-developed, by at least one GCIG Group. Any industry sponsored 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.

Checklist:

- Identification of GCIG group(s) involved in protocol development
- must be more than one GCIG member group participating to be a GCIG trial; identification
- Identification of cooperative group members involved in development, including group statistician
- Identification of non-industry sponsorship (investigator-initiated but allowing for industry funding but requires sponsorship by non-industry vs industry-sponsored)

2. Trial peer review

GCIG trials should have been 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 a Trial Steering/Leadership Committee, which includes independent membership, independent Protocol Review Committee (or equivalent) to scrutinise the protocol and sign it off before the trial opens.

Checklist:

- Demonstration of independent peer review, such as: government funding agencies, academic institutional scientific and clinical trial review
- Transparent primary clinical trial leadership and per GCIG-group trial leadership
- Confirmation of review by Protocol Review Committee
- Confirmation of Data Management Committee (GCIG has a policy)

3. Sponsorship/Funding

Investigator-initiated trials may be wholly by industry. In such cases, the sponsorship, eg regulatory responsibility for the clinical trial, is not with the industry funder, but with the investigator/program/institution. An industry-sponsored (and funded) study is developed by industry and carries the sponsor's legal responsibilities and industry-defined leadership for the study. Such studies are not optimal GCIG studies and do not fall within the above definitions.

Checklist for industry funded studies (wholly or in part)

- Identification of non-industry study regulatory sponsor
- If sponsor is pharma, confirmation by both sponsor and lead group/groups that this is an investigator-initiated study, fulfilling the GCIG principles of independence

4. Conduct/Control of the Trial

In the case of non-industry sponsorship, the trial should be led by a GCIG Group, which controls the trial conduct and the analysis. The Data Monitoring Committee must receive at least annual progress reports on accrual and safety from the Steering Committee or trial leadership. When GCIG Groups collaborate, after final analysis, the data must be accessible to all participating Groups with the involvement of the lead Group. All collaborating Groups and co-investigators must understand, document, and comply with Good Clinical Practice.

Checklist

- Identification of lead GCIG group
- Evidence of regular DMC meetings (to occur at least annually, regarding accrual and safety.)
- Confirmation that data will be available to all groups with involvement of lead group . This should this be signed document before the study starts.
- Evidence of compliance with GCP (could be whatever individual countries or groups require) including evidence of monitoring/auditing expectations.

5. Data Management

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

Checklist

- Identification as to where data is held and who controls it. Must NOT be CRO nor Pharma
- If registration trial, formal agreement with industry partner to be provided outlining access arrangements to database.

6. Trial Analysis (including interims and futilities)

In the case of investigator initiated trials (with or without industry funding), the analysis will be defined in the protocol. In the case of an Industry sponsored trial, the trial will be analysed by an independent statistician on behalf of an Industry sponsor, and only when the data are sufficiently mature. Whenever possible, the analysis should be undertaken by the Industry sponsor in co-operation with the lead study group. The analysis should be seen by the Data Monitoring Committee.

Checklist

- Identification of independent statistician, who will determine timing of analysis.
- Confirmation that the analysis will be/has been seen by the DMC
- Contract with industry group clearly states that trial analysis is the responsibility of the lead GCIG group

7. Reporting of the trial

The trial should be reported independently of the funding industry sponsor. The final draft (presentation/manuscript) may be shared with the 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.

Checklist

- Contract with industry group clearly states that trial reporting is the responsibility of the lead GCIG group
- Authorship agreed by all collaborators at outset, and publication agreement provided (CRITICAL)

SUMMARY CHECKLIST:

- Identification of GCIG groups involved in development (may be more than one)
- Identification of clinical trials group members involved in development, including group statistician
- Identification of participating and lead GCIG Groups (must be more than one to be a GCIG trial).
- Identification of non-industry sponsorship
- Identification of study sponsor (Lead)
- Demonstration of independent peer review, such as: government funding agencies, academic institutional scientific and clinical trial review
- Transparent primary clinical trial leadership and per GCIG-group trial leadership
- Identification of protocol review Committee members
- Identification of DMC (GCIG has a policy)
- Identification of non-industry study regulatory sponsor

- If sponsor is pharma, confirmation by both sponsor and lead group/groups that this is an investigator-initiated study, fulfilling the GCIG principles of independence
- Evidence of regular DMC meetings must be provided to GCIG (to occur at least annually, regarding accrual and safety.)
- Confirmation that data will be available to all participating groups with involvement of lead group. This should be signed documentation before the study starts.
- Evidence of compliance with GCP (could be whatever individual countries or groups require) including evidence of monitoring/auditing expectations.
- Identification as to where data is held and who controls it. Must NOT be CRO nor Pharma
- If registration trial, formal agreement with industry partner to be provided outlining access arrangements to database.
- Identification of independent statistician, who will determine timing of analysis.
- Confirmation that the analysis will be/has been seen by the DMC
- Contract with industry group clearly states that trial analysis is the responsibility of the lead GCIG group
- Authorship agreed by all collaborators at outset, and publication agreement provided.