GCIG PRINCIPLES OF INDEPENDENCE **version May 2020**

Principles of Independence Governing GCIG Clinical Trials

The foundation of this has been directly taken from the November 2018 draft document and updated/revised.

The GCIG has been in existence since 1993 (founded), 1997 (formally), 2011 (incorporated), and during the last 24 years has participated in 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, as such, called Academic trials. Others have been partially funded by industry with data ownership by the Academic Group (Academic trial), and in some cases, completely designed, run, funded and sponsored by industry, with the database belonging to the industry sponsor, as such, called Industry trials.

This paper sets out a number of criteria, which are required as a means of ensuring that the criteria for the conduct of GCIG studies and the adherence to GCIG membership parameters are being met in a way that guarantees independence and transparency. It was proposed at the 2015 GCIG Strategic planning meeting that a prospective checklist be developed, and be used before trials are GCIG- badged, to ensure adherence to GCIG criteria.

Any attempt to define principles governing GCIG activity needs to recognise that GCIG Member Groups (currently thirty-three) come from North America, Europe, Australia/New Zealand and Asia. Each country or group of countries has its own rules and regulations regarding clinical trials [e.g. 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 regard to funding sources. 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.

Membership currently requires participation in at least two GCIG-badged trials. It has become necessary to define what constitutes a GCIG-badged trial, and use of the subcategories of

"Academic" and "Industry-sponsored" are proposed in recognition of the above mentioned complexities and the profusion of trials fully sponsored and owned by Industry.

The GCIG will adopt the definitions of the categories of ENGOT "A", for the Academic trials and ENGOT "C" for the Industry-sponsored studies. GCIG gives the highest priority for badging and Academic/ "A" trial for full Group membership recognition. Any number of *GCIG-badged* Industry-sponsored/ "C" trials will suffice for the second trial participation.

GCIG recognizes that some of its provisional and newer members may not yet have the infrastructure and/or funding to participate in an Academic/ "A" trial, and will define, under separate cover, criteria for continued InterGroup participation for such members.

GCIG recognizes the need to be able to partner with industry in clinical trials. At the same time, GCIG must be able to demonstrate that Industry-sponsored/ "C" trials have been appropriately designed, conducted, analysed and reported in order to justify the GCIG approval for badging (see below).

The GCIG embraces translational research as an important part of any clinical trial and strongly supports collection of appropriate specimens. Translational plans can be addressed at any time in clinical trials (prior or during or after the end of the trial), and such plans need to be a collaboration between the sponsor and the GCIG participating groups.

The following seven principles cover requirements for GCIG trial-badging as pertains to trial development, peer review, sponsorship, conduct, data collection/database ownership, analysis and reporting.

1. Trial Development

GCIG trial protocols must be developed or at least co-developed, by at least one GCIG Group. Co-development of a protocol by the lead GCIG study group with industry can be considered for badging an Industry-sponsored/"C" labelled study.

Checklist:

1. Feasibility assessment;
2. Identification and documentation of participation of GCIG group(s) in protocol development;
3. Involvement and concurrence by the GCIG group statistician, prior to badging request, on the Statistical Analysis Plan, if an Industry-sponsored/ "C" study or registration study of any kind;
4. Transparent designation of primary clinical trial leadership and per GCIG-group trial leadership, and where indicated, Trial Steering Committee and its constitution.

2. Trial peer review

GCIG trials must undergo peer review to guarantee the scientific validity of the study, feasibility of completion in a timely fashion, and for transparent identification and review of conflict(s) of interest.

Checklist:

1. Demonstration of independent peer review, such as: government funding agencies, academic institutional scientific and clinical trial review by lead Group (in the case of an Industry-sponsored/ "C" trial;
2. Feasibility assessment;
3. Conflict of interest assessment.

3. Sponsorship/Funding

Sponsorship is defined as who has the regulatory and pharmacovigilance responsibility and holds final data property. It is recognized that Academic/ "A" studies (Investigator-initiated) may be funded in part or in whole by industry, if the responsibility and data ownership lay with the Academic group. The regulatory and pharmacovigilance responsibility for Industry-sponsored/ "C" studies, funded by industry, is with the Industry leader.

Checklist for sponsorship and funding:

1. Identification of study regulatory sponsor: Academic or Industry;
2. Review of the financial and non-financial incentives for participation and recruitment demonstrating equipoise, no conflict of interest and no introduction of Industry bias;
3. Documentation of funding parity across participating groups in Industry-sponsored/ "C" studies;
4. Detailed management of the entire trial including the role of the CRO and its relationship with the company and the GCIG group.

4. Conduct/Control of the Trial

All trials, whether Academic or Industry-sponsored, should have the necessary and appropriate regulatory, safety, pharmacovigilance, conflict of interest, and data management oversight. This should be clearly defined in the protocol, and be independent of the trial leadership and sponsorship.

Checklist for conduct and control:

1. At least two GCIG member groups commit to participation and have necessary elements (oversight, funding, etc) as required for participation;
2. All participating Groups and Investigators are current in Good Clinical Practice training and National requirements;
3. Prospective definition and constitution of an IDMC if one does not already exist within Lead Group structure; this IDMC ideally should include membership from all GCIG-participating Groups (or a majority of such, if broad participation) and prospective determination of frequency of reviews;
4. Confirmation of database ownership and prospective plan agreement on data access and database copies. More than one database is allowed in the situation that regional regulatory obligations make one trial with merged databases logistically preferable to a single database (e.g. such as in some cases of collaboration with the NCI NCTN);

5. Prospective determination and contractual documentation of responsibility for the pharmacovigilance database and responsibility to regulatory authorities and participating Groups/Sites for reporting SAE;
6. Registration and details on clinicaltrials.gov.

5. Data Management, Monitoring, and Database Access

It is recognized that trials may vary from single arm phase 2 through registration-targeted phase 3 trials. Pharmacovigilance, monitoring, and database design needs will vary according to type of trial, number of collaborating Groups, and sponsorship. It is required, in the case of Industry-sponsored/ "C" studies, that prospective agreement be made allowing database access by the GCIG lead study group for meta-analysis upon mutual agreement after primary endpoint results are published.

Checklist for data management, monitoring and database access:

1. Prospective identification of the Data Management Plan (Academic center/GCIG Group, CRO) with confirmation of the ownership of the database as defined above (Academic/ "A": center or Group; Industry-sponsored/ "C": pharma with access by Lead GCIG Group after primary endpoint is met);
2. Prospective documentation of CRF plan, preferentially a single Web site-based electronic case report form;
3. Prospective identification of the study-appropriate monitoring plan and responsibility for monitoring and reporting;
4. Prospective agreement defining access to data, when, and to whom, and protecting the primacy of the data until the primary endpoint is met.

6. Trial Analysis (including interims and futilities)

The analysis plan, including interim futility and efficacy analyses, should be prospectively planned in the final protocol document and/or SAP. See also #1 Trial Development defining metrics for SAP approval in the case of Industry-sponsored/ "C" trials. The analyses 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 for trial analyses:

1. The Industry-sponsored/ "C" trials should have a prospective agreement that analyses should be undertaken by the Industry sponsor in cooperation with the study group statistician;
2. Prospective plan that the analyses will be presented to the IDMC, followed by the lead GCIG study group upon IDMC agreement to release the data, prior to public data release.

7. Reporting of the Trial

Checklist:

1. The lead GCIG group has responsibility for negotiating a prospective plan indicating recognition of participating groups for publication purposes (# authors, location of authorship, first/last);
2. Prospective agreement that study results will be published, ***irrespective of outcome;***
3. Prospective agreement to identify study type in all publications (Academic/"A" v Industry-sponsored/ "C").

SUMMARY CHECKLIST FOR INITIAL BADGING APPROVAL:

Note: Badging approval requires approval by a 2/3 majority of the Board of Directors, with a minimum 70% quorum voting. This voting can be done by email and will be tabulated in the GCIG Operations office. Any member of the Board of Directors may request the Executive Committee review of Badging decisions at the initial badging determination at the initiation of a protocol, or at any time during protocol execution if there are concerns regarding study conformation to these principles.

1. Badging approval checklist prior to activation of trial (consolidation of checklists above);
2. Feasibility assessment;
3. Identification and documentation of participation of GCIG group(s) in protocol development;
4. Involvement and concurrence by the GCIG group statistician, prior to badging request, on the Statistical Analysis Plan, if an Industry-sponsored/ "C" study or registration study of any kind;
5. Demonstration of independent peer review, such as: government funding agencies, academic institutional scientific and clinical trial review by lead Group (in the case of an Industry-sponsored/ "C" trial);
6. Feasibility assessment;
7. Conflict of interest assessment;
8. Identification of study regulatory sponsor: Academic or Industry;
9. Review of the financial and non-financial incentives for participation and recruitment demonstrating equipoise, no conflict of interest, no introduction of Industry bias;
10. Documentation of funding parity across participating groups in Industry-sponsored/ "C" studies;
11. Detailed management of the entire trial including the role of the CRO and its relationship with the company and the GCIG group;
12. At least two GCIG member groups commit to participation and have necessary elements (oversight, funding, etc) as required for participation;
13. All participating Groups and Investigators are current in Good Clinical Practice training and National requirements;
14. Prospective definition and constitution of an IDMC if one does not already exist within Lead Group structure; this IDMC should include membership from all GCIG-participating Groups

(or a majority of such, if broad participation) and prospective determination of frequency of reviews;

15. Confirmation of database ownership and prospective plan agreement on data access, database copies. More than one database is allowed in the situation that regional regulatory obligations make one trial with merged databases logistically preferable to a single database (e.g. such as in some cases of collaboration with the NCI NCTN);
16. Prospective determination and contractual documentation of responsibility for the pharmacovigilance database and responsibility to regulatory authorities and participating Groups/Sites for reporting SAEs;
17. Registration and details on clinicaltrials.gov;
18. The Industry-sponsored/ "C" trials should have a prospective agreement that analyses should be undertaken by the Industry sponsor in cooperation with the study group statistician;
19. Prospective plan that the analyses will be presented to the IDMC, followed by the lead GCIG study group upon IDMC agreement to release the data, prior to public data release;
20. The lead GCIG group has responsibility for negotiating a prospective plan indicating recognition of participating groups for publication purposes (# authors, location of authorship, first/last);
21. Prospective agreement that study results will be published, *irrespective of outcome;*
22. Prospective agreement to identify study type in all publications (Academic/ "A" v Industry-sponsored/ "C");