[TRIAL LOGO] [LEAD AND COLLABORATING GROUP LOGOS]

LEAD GROUP: [NAME]

COLLABORATING GROUP: [NAME]

GROUP-SPECIFIC APPENDIX (GSA) FOR

[SHORT NAME OF TRIAL]

[FULL TRIAL TITLE]

Disclaimer

The GSA may be adapted and used according to the needs of the trial and the requirements of the country. An agreement must be made between the Lead Group and the Collaborating Group regarding the purpose of this document:

- an appendix to the Main protocol (submitted for appropriate approvals)
- an appendix to the Contract (Intergroup Agreement)
- as an operational guide only

Revision History

Version	Author	Date	Reason for amendment
1	Laura Farrelly	16Feb2013	Version 1
2	Laura Farrelly	25Feb2014	Version 2 • Following GCIG London meeting, it was decided to change the title of the document from Protocol Appendix to Operating Procedures, as this describes the document in a clearer way. • Minor formatting changes made throughout document
3	Laura Farrelly	4Mar2015	Version 3 • Following discussions regarding publication of paper and a survey amongst users, it was decided to revert to GSA (Appendix) – and give GCIGs the choice of being an appendix to the protocol or the agreement • Additional headers included – formatting of title emphasis for index • Disclaimer added regarding use of document • All sections updated

1. TRIAL ORGANISATION

This trial is a collaboration between:

[Lead Group name]
[Collaborating Group name]

The [Lead group name] is the lead coordinating centre for the trial. The [Lead group] is responsible for the overall trial conduct (including protocol finalisation, trial activation, data management, statistical analysis and publication).

The [collaborating group], *represented by the [Name of Legal Sponsor]* is the coordinating centre of the trial in [collaborating group country] and through [*Name of Legal Sponsor*] will manage the conduct of the study in [collaborating group country] in collaboration with the [Lead group]. The [collaborating country] and [lead group] are responsible for academic leadership of the trial in [collaborating group country].

[Collaborating group country] sites must refer to the **current** approved [Trial name] study protocol developed by the [Lead group] for conducting the study at their site. This [Collaborating group] Group-Specific Appendix includes additional information about trial conduct in [collaborating group country].

- The following duties will be undertaken by the [collaborating group] for their sites:

    - Coordinating national and local ethics and regulatory submissions
    - Collecting regulatory documents;
    - Providing supporting documentation to [lead group]
    - Establishing a local Trial Management Committee (TMC)
    - Primary contact to [collaborating group] sites for all queries
    - Disseminating study information and reports to all [collaborating group] sites as required
    - Conducting site initiation meetings and site activation
    - Local monitoring
        - Monitoring local recruitment and protocol compliance
        - Ensuring timely CRF completion
        - Ensuring timely query resolution
        - Collecting any paper Case Report Forms (CRFs).
        - Onsite monitoring.
    - Managing site payments
    - Overseeing SAE reporting, collecting and forwarding SAE forms/reports to the [lead group]

- [collaborating group] investigators will use the SAE definition as stated in the protocol
- [collaborating group] investigators will use the [lead group] SAE form which will be paper based

1.01 SPONSOR

[XXX] is the legal sponsor in [collaborating group country(ies)]

Please state the sponsor institution and agreed terminology (e.g. if sponsor outside EU then who within EU is the EU legal representative.

Provide details regarding whether the [collaborating group] named in the GSA is called a country representative, EU representative, local sponsor or other title in their own country.

1.02 TRIAL DRUG SUPPLY (IF APPLICABLE)

- Licensing status of IMP in the [collaborating group] country
- Details of supplier
- Details of drug supply to site
- Details of import license
- Details of re-supply

1.03 TMG (TRIAL MANAGEMENT GROUP)

Meetings will be organised by the [lead group] trial unit's team. A TMG charter will be produced by the [lead group] and appropriate signatures will be collected from the [collaborating group] members.
[Collaborating group] membership will consist of the [collaborating group] CI and co-coordinating centre staff as appropriate.

- Details of regularity (including teleconference and face-to-face meetings)

1.04 TMF (TRIAL MASTER FILE)

The Collaborating Group is responsible to set-up and maintain a Trial Master File (TMF) containing documents and written communications essential to the management of the study. All documents to be filed in the TMF according to ICH GCP requirements must be clearly identifiable.

In case of audits or inspections, Collaborating Groups may have to centralise the TMF to the Lead Group/Sponsor. Lead Group/Sponsor will return all documents owned by the Collaborating Group as necessary.

The TMF must be kept in a secure location for the duration of the study and archived after completion or premature termination of the study in a secure fire-proof facility for the required length of time depending on local/national regulatory requirements and taking into consideration trial time-lines (usually a minimum of 15 years).

In the EU
The Clinical Trials Regulation EU No 536/2014 (875 KB) will become applicable when the current Directive is repealed on the day of entry into application of the Clinical Trial Regulation. It will however still apply three years from that day to:
◦Clinical trials applications submitted before the entry into application (no earlier than 28 May 2016)
◦Clinical trials applications submitted within one year after the entry into application if the sponsor opted for old system.
Therefore, at the earliest (28 May 2016) a minimum of 25 years for archiving in MS will apply.

2. INVESTIGATOR AUTHORISATION PROCEDURE

Investigators will be authorised to randomise patients in this trial only when they have returned the following regulatory documents to the [collaborating group] – amend as necessary:

- Copy of the [describe here Ethics Committee opinions and regulatory authorities approvals needed prior to the start of the trial as applicable]
- Signed Principal Investigator Agreement

- Copy of the approved Participant Information Sheet and Consent Form(s)
- Delegation of Authority (Signature Log) signed by all involved staff
- Copy of current laboratory normal ranges
- Copy of current laboratory accreditation
- Pharmacy contact details form
- Investigators' and co-Investigator's Curricula Vitae, signed and dated
- Financial disclosure forms signed by all the investigators
- Copy of the site checklist

2.01 REGULATORY DOCUMENTATION

REGULATORY DOCUMENTS SHOULD BE SENT TO THE [COLLABORATING GROUP] COORDINATING CENTRE AT THE FOLLOWING ADDRESS:

[Trial name]
[Collaborating group address]

2.02 CENTRE SPECIFIC REQUIREMENTS FOR LOCAL ACTIVATION

Site staff must either attend an investigator initiation (start-up) meeting or a trial initiation teleconference with the [collaborating group] [trial name] Trial Coordinator prior to activation (as per local practice).
The [Lead group] will be immediately informed of each authorised investigator and will conduct the final approval of each site.
An activation letter will be sent to each site once all regulatory and study specific training requirements have been met.

3. PATIENT REGISTRATION & RANDOMISATION PROCEDURE

Refer to main protocol (as applicable)

3.01 UNBLINDING (IF APPLICABLE)

3.02 GP LETTER (IF APPLICABLE)

A template GP letter for notifying the patient's GP of their participation in the [trial name] can be found in the Investigators folder.

4. STUDY PROCEDURES AND START-UP SUPPLIES

List any specific study procedures here (e.g. Blood pressure monitoring) and how they will be obtained/shipped (as applicable)

5. DATA COLLECTION AND QUERYING PROCEDURES

- The [lead group] is responsible for all querying (other than queries arising from on site monitoring), cleaning, and analyses.

Indicate what form the data collection will follow (e.g. 'mail-box' procedure at collaborating group co-ordinating centre using paper based forms, or eCRFs/EDC).

If paper based; the data will be reported on [trial name] specific case report forms (CRFs). All the Investigators participating on behalf of [collaborating group] will send all the forms to:

[Address here]

"mail-box" procedure for paper CRFs

- Signed original CRFs will be collected by the [collaborating group] Coordinating Centre and sent regularly to the [lead group] according to the form flow schedule (provided with the CRFs).
- Investigators will/will not be allowed to send CRFs directly to the [lead group].
- The [collaborating group] Coordinating Centre will not modify the forms nor enter them into the computer (or database)
- The [lead group] will enter the data and perform quality control and analysis.

When necessary, queries will be transmitted to the [collaborating group] Coordinating Centre, which will send them to the investigators. The [collaborating group] Coordinating Centre will then send the reply of the investigators back to the [lead group].

5.02 CASE REPORT FORMS (CRFS), SUBMISSION SCHEDULE AND DATA QUERIES

Study Period	Timelines for entry of all required data in the CRF	Timelines for resolution of Data Queries	Timelines for shipping completed CRFs to [lead group] for data entry

*The critical study periods should be indicated where necessary (i.e. at times of IDMC meetings or analyses).

The list of forms to be completed for this study and their submission schedule is in the main protocol and in the CRF completion guidelines.

5.03 DATA QUERYING PROCEDURE TO BE DETAILED HERE BY [LEAD GROUP]

5.04 OTHER SUB STUDY FORMS AND ALL RELEVANT SUPPORTING DOCUMENTATION

All sub study forms and relevant supporting documentation (e.g. copies of pathology reports, radiology etc) as discussed in the main protocol should be sent to the [collaborating group] Coordinating Centre (and NOT directly to the [lead group]), a copy of these documents must be kept at the site.

These documents should be sent to the following address:

[Collaborating group address here]

IMPORTANT NOTE: SAE-related queries must be answered and returned to [collaborating group] by fax within 24 hours as per the safety reporting procedures in section 6.

6. SAFETY REPORTING

All [collaborating group] investigators will use the same definitions as defined in the main protocol (Ref here)

6.01 SERIOUS ADVERSE EVENTS

SAEs occurring from the time a subject is registered/randomised until xx days after last protocol treatment must be promptly reported. Any SAE occurring after the xx-days period and considered to be reasonably related to the investigational product or study participation, also have to be promptly reported.

SAEs must be reported **by (select mode e.g. fax in this example)** to the **[collaborating group]** and to the **[Lead group] (this may be done by either the site or the collaborating group depending on the agreement)** on a Serious Adverse Event Form **within 24 hours** of the initial observation. **[Collaborating group]** sites will complete the fax cover sheet provided by the **[collaborating group]** and fax along with the SAE form to the number(s) below:

[Collaborating group country] Fax details

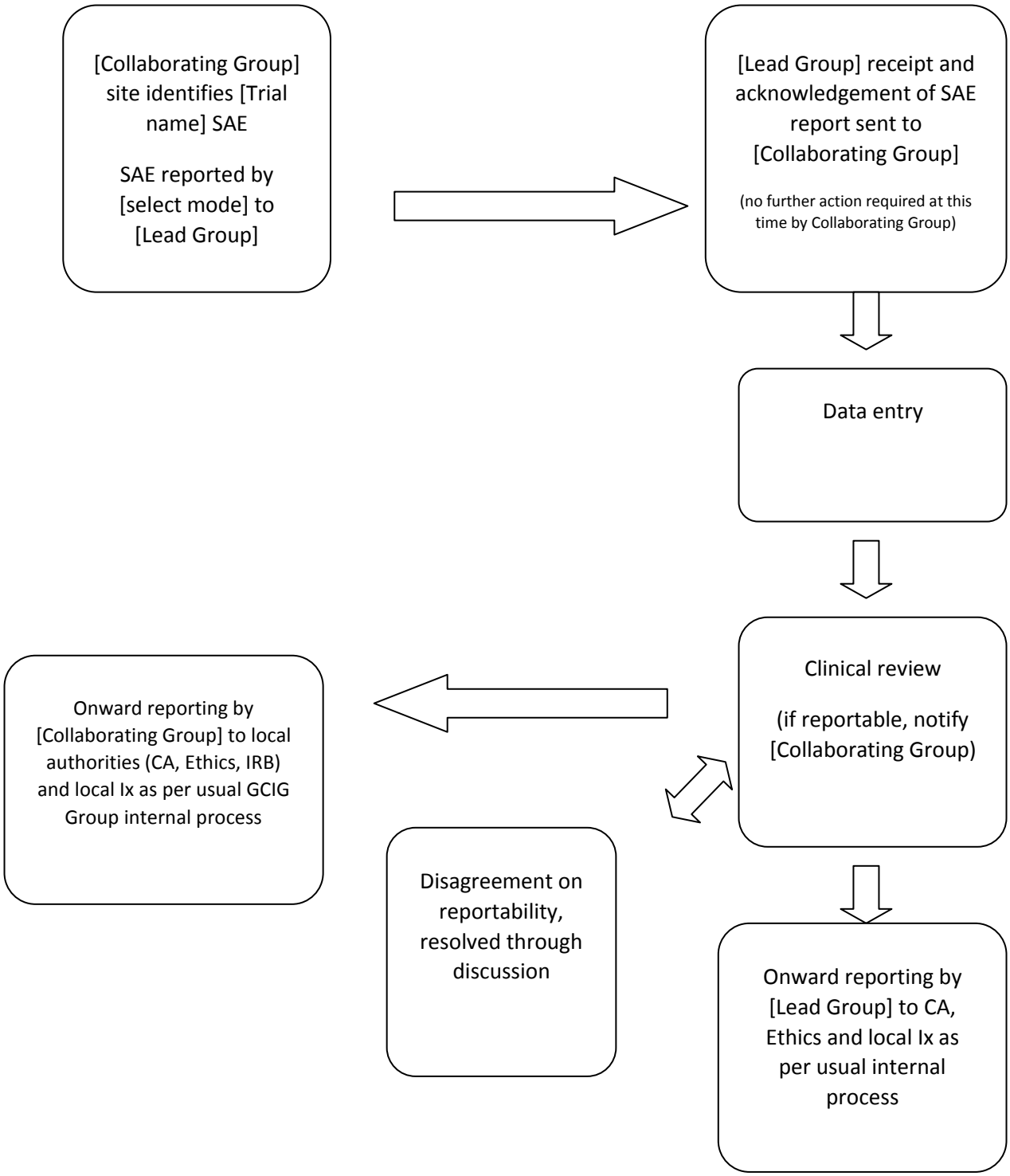
AND/OR

[Lead group country] Fax details

The original SAE-form must either be retained or returned to the **[collaborating group]** within 10 days of the initial observation of the Serious Adverse Event.

Further guidance on safety reporting in the [trial name] (including reporting of pregnancies) is provided in section xx of the trial protocol and in the SAE Form Completion Guidelines.

Serious Adverse Event Flow Diagram for GCIG sites



SUSARs that occur at [collaborating group] sites will be unblinded (if necessary) by [lead group] Trial staff and a CIOMS report will be generated. If these require onward reporting to regulators the [lead group] team will forward them by fax or e-mail as appropriate to the [Collaborating group] for onward reporting to fulfill regulatory requirements in [collaborating group country].

Timelines for reporting are as follows: 7 days for SUSARs with fatal outcome or life-threatening; 15 days for all other SUSARs.

Email address for SUSAR reporting in [collaborating group country]:
Fax no. for SUSAR reporting in [collaborating group country] :

If applicable, in case of disagreement on the decision regarding SUSAR assessing (for SAEs occurring in [Collaborative Group Country]), the worst assessment will prevail

Trial SAEs that are considered both related and unexpected (Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring in other collaborating countries will be forwarded electronically to [collaborating group] either immediately or on a [*6-monthly]* basis (depending on the country requirements). [Collaborating group] will then be responsible for disseminating to all local sites as required.

For example: In UK (adjust as necessary for [lead group country]
All countries SUSARs will be reported by the [lead group] via eSUSAR (or applicable reporting channel).
The MHRA submits SUSARs occurring in UK, and third country (those being outside the EEA) via the MHRA's eSUSAR website to the European Medicines Agency's (EMA's) EudraVigilance Clinical Trial Module (EVCTM) Onward reporting to other countries Competent Authority must be completed by each Collaborating Group.
For Pan-European trials one European group should be responsible for eReporting to EVCTM. This needs to be clarified between the European GCIGs.

{Collaborating group] will collaborate in the resolution of the follow-up questions to the SAE reports, by forwarding them to the Investigators, channelling their responses back to [Lead group] and by providing data as required when needed for the resolution of the queries.

[Collaborating group] will confirm with [Lead group] when communicating safety information to investigators, central Ethics Committees and National Authorities, in order that [lead group] can file track reporting in the central [Trial name] safety information file.

The Development Safety Update Report (DSUR) will be prepared annually for safety information collected over the period of one year starting from the date of the first regulatory approval granted (***CTA approval dated*** *dd/mmm/yyyy*). The Annual DSUR will be submitted to [Lead group] Regulatory/Competent Authority and Ethics Committee within 60 days of the anniversary of this date. A copy of this report is sent to [Collaborating group]. [Collaborating group] is responsible for onward reporting of this document according to their national and local regulations.

CONTACT PERSON FOR SAFETY DATA FLOW AT [Lead group]:

CONTACT PERSON FOR SAFETY DATA FLOW AT [Collaborating group]:

7. MONITORING

Central monitoring details here (or refer to Monitoring Plan)

- Monitoring visits at study sites will be conducted by the **[collaborating group]** Coordinating Centre according to the [Trial name] Monitoring Plan.
- **[collaborating group]** will review paper CRFs for completeness and errors (queries will generated by the [lead group]), will monitor timely data (CRF) flow from sites to [lead group], will facilitate the movement of queries to site from [lead group] and back again, will establish and maintain a positive relationship with sites.
- All AEs and SAEs will be tracked and facilitated from site to the [lead group] according to the [trial name] monitoring plan.
- Details of monitoring specific to [trial name] here: (for example below}
  - All patients will SDV'd 100% for the following; eligibility variables including consent, eligibility/ ineligibility including lab values, disease and date of progression, date and cause of death. If applicable they will also be SDV'd 100% for trial SAE/SUSAR, drug discontinuation or interruptions, and a random proportion of patients at each site will be checked for grade 3 or 4 toxicities.
  - The ISF will be checked centrally against a checklist and confirmed at site visit.
  - Pharmacy: 100% SDV of trial drug dispensing/prescriptions will be compared to the IVRS web reports (if used)

8. ADMINISTRATIVE RESPONSIBILITIES

8.01 [COLLABORATING GROUP] CI

The **[collaborating group]** Chief Investigator (CI) is Dr [name here], who will be responsible for clarifying protocol-specific and associated medical questions, and for overseeing satisfactory trial conduct in **[collaborating group country].** All queries to Dr [name here] should first be submitted to the **[collaborating group]** Coordinating Centre who will forward these to Dr [name here]. Requests regarding eligibility or unblinding must also be discussed with a [lead group] CI or trial physician, before being granted.

8.02 THE [COLLABORATING GROUP] COORDINATING CENTRE

The **[collaborating group]** Coordinating Centre is responsible for handling regulatory requirements and overseeing the conduct of the study in **[collaborating group country].** The [**collaborating group]** Coordinating Centre will act as primary contact for all **[collaborating group]** sites, and as an intermediate guaranteeing communication between the [lead group] and the investigators participating on behalf of the [**collaborating group]**.

[Collaborating group] Coordinating Centre
Address
Phone:
Fax:

[Trial name] Trial Coordinator
[Name here]

Tel:
Fax:
E-mail:

9. AUDITS

Audits may be conducted by the **[collaborating group]**, the [lead group] (or their agents), national and/or foreign regulatory authorities or the pharmaceutical company supplying the investigational drug for the study [name of pharma here if applicable]).

The investigator, by accepting to participate to this protocol, agrees to cooperate fully with any quality assurance visit undertaken by third parties, as well as to allow direct access to documentation pertaining to the clinical trial (including CRFs, source documents, hospital patient records and other study files) to these authorised individuals.

In some instances, the Quality Assurance plan for the trial will be referenced in the protocol only and saved as a separate document (please specify if this is the case).

10. SUB-STUDIES

10.01 TRANSLATIONAL STUDY (SPECIMEN COLLECTION)

[Collaborating group] participation in the translational study is [mandatory unless patients refuse to consent to the sub-study] or [subject to agreement]. Patients can participate in the clinical study if they refuse to participate in the translational study.

List any specific details of the translational study here.

10.02 QUALITY OF LIFE

10.03 HEALTH ECONOMICS

11. TRIAL SPONSORSHIP AND INSURANCE

DETAILS OF SPONSOR HERE (EITHER [LEAD GROUP], DELEGATED DUTIES OF SPONSOR TO [COLLABORATIVE GROUP] OR OTHER

If the collaborating group have delegated sponsorship duties use the sentence below:

The [xxx] has been delegated some duties of the sponsor for the trial in the [collaborating group country] in its capacity as the legal entity representing the [lead group].

The [collaborating group] is responsible for the conduct of the study in [collaborating group country] under the auspices of [Lead group].

IF ACADEMIC SPONSOR:

[Trial name] is an investigator initiated collaborative group study for which there is no industry sponsor designated to provide indemnity for the trial. Therefore each participating centre must provide its own indemnity for the study. Mutual indemnity arrangements are as set out in the investigator agreement between the participating centres and [collaborating group or affiliated university].

All employees of the [collaborating group] are covered by professional indemnity; however this may not extend to other personnel conducting the trial at the participating centres (please check).

If pharmaceutical sponsor (or where applicable):sponsor has contracted the clinical trial insurance in compliance with the applicable legislation.

12. ETHICS AND REGULATORY COMPLIANCE

This study will be conducted according to the [principles of ICH GCP in member states] / [insert other GCP and laws and regulations as applicable]. In case of conflict between these regulations, national statutory law prevails.
The investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a subject. In this circumstance the [collaborating group co-ordinating centre], principal investigator and ethical body must be advised immediately.

12.01 RESEARCH ETHICS COMMITTEES

The protocol, patient information sheet and informed consent form and quality of life instruments must be approved by a National Ethics Committee (as applicable) in compliance with Good Clinical Practice and applicable regulatory requirements. A copy of the written approval/advice must be sent to the [collaborating groups co-ordinating centre], outlining the documents approved (protocol, patient information sheet and informed consent form, and quality of life) and the version and date of approval. A copy of the approved patient information sheet and informed consent should also be sent to the [collaborating groups co-ordinating centre].
If there are any version changes to the patient information sheet or informed consent forms, these must be submitted to the [collaborating groups co-ordinating centre] for review PRIOR to use.
Ethics committee composition must comply with the above local regulatory guidelines.
Annual re-approvals should only be provided if in accordance with local ethics procedures; otherwise local ethics progress report submission confirmation should be provided to the [collaborating groups co-ordinating centre] who will forward this to the [lead group].

12.02 REGULATORY GUIDELINES

World Medical Association Declaration of Helsinki
Ethical Principles for Medical Research Involving Human Subjects
http://www.wma.net/e/policy/b3.htm

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)
http://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

EU directive
http://ec.europa.eu/health/documents/eudralex/vol-10/

13.CONFLICT OF INTEREST

Conflict of interest (If not described in the protocol / If required in the country)

With regards to the conflicts of interest (COI) in this trial, the self-declaration forms submitted by investigators should be reviewed and approved by [list required approvers] before initiation of the study and when publishing/presenting results [if applicable].

14. FUNDING FOR TRIAL

This trial is conducted with main financial support from [Lead Group or Industry] in [Country]. Research funds from [complete as appropriate] also partially support this trial.

15. AUTHORSHIP

Authorship of research papers produced based on this trial will generally be determined as follows:

[Please select most appropriate to your trial]

- the first author of the main research paper will be [Lead Chief Investigator /Study Chair and the following multiple authors will be determined in order of their degree of contribution in the trial with consensus among the group representatives]

Or

Internationally agreed authorship guidelines published by JAMA and the international committee of journal editors state that authorship should be based on 3 criteria, all of which need to be met:

- substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data
- drafting the article or revising it critically for important intellectual content
- final approval of version to be published

All persons designated as authors need to fulfil all authorship criteria, and all those who fulfil the criteria should be named as authors.

(example from ICON7)

The final agreed Writing Committee membership for the main (PFS and OS) publications are as follows:

International Lead and Co-Lead CIs (2)

Main Representatives from each [collaborating group] (7)

Additional representatives from groups based on recruitment 1 place for each 100 (10 to 15)

[Lead Group] scientists (3)

Additional members may be proposed and agreed by the TMG

Order of Writing Committee Members

Publication description	**1st**	**2nd**	**3rd**	**Last**	**Others**
Primary publication PFS and OS	**Lead CI**	**Lead Group Representatives**	**GCIG rep with highest recruitment**	**Co Lead CI**	**in order of recruitment**