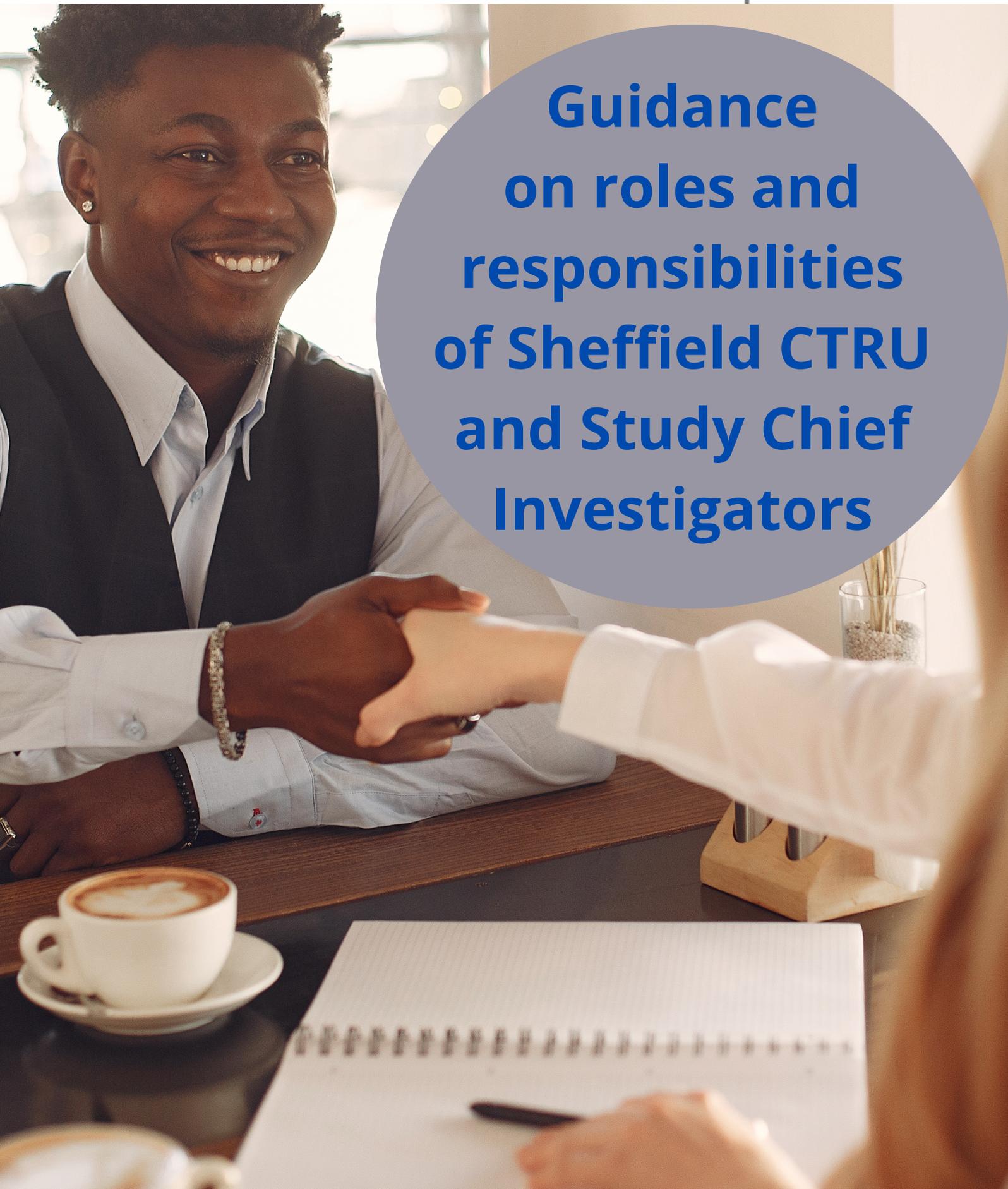


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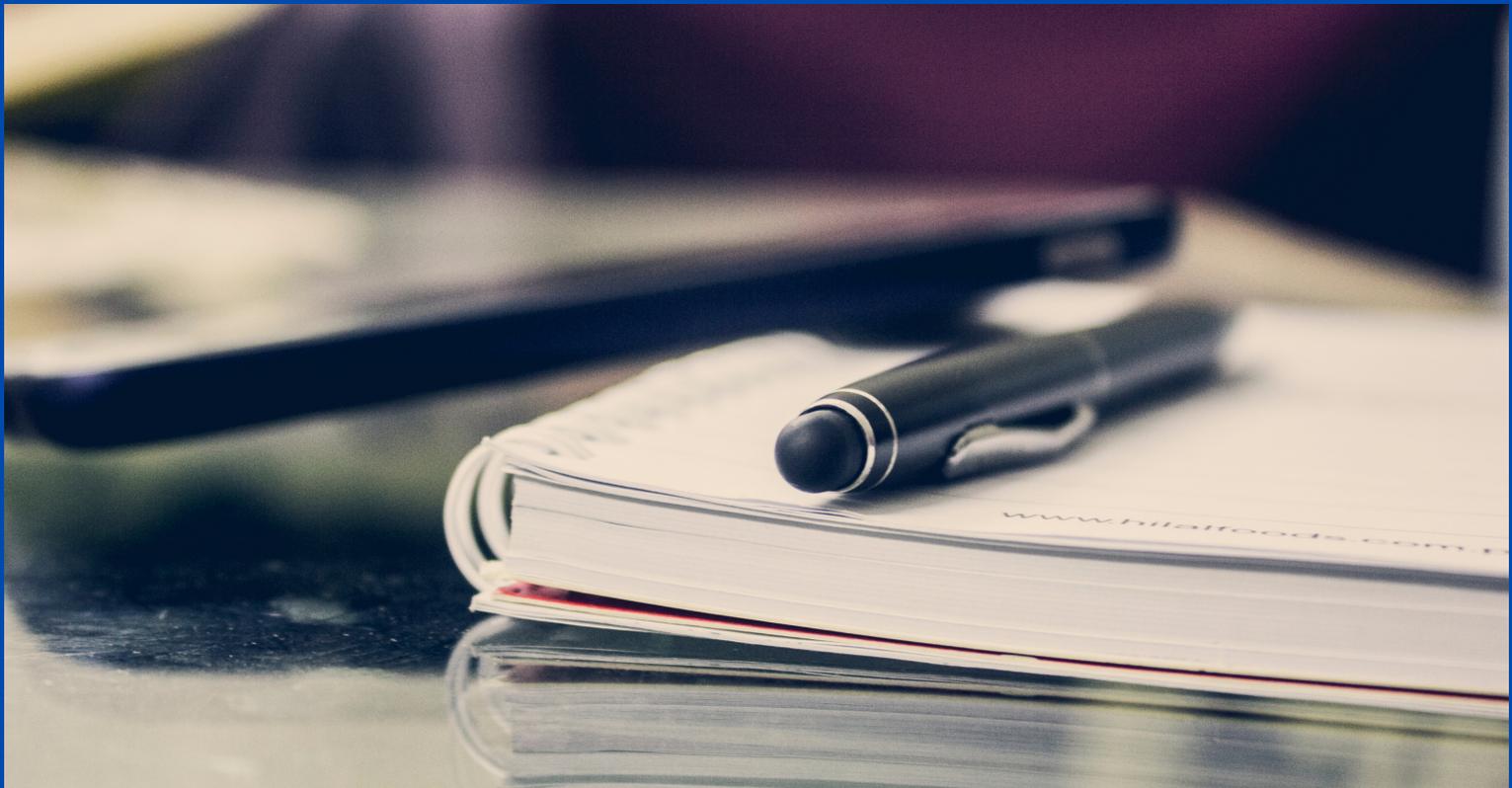
Clinical
Trials
Research
Unit.



**Guidance
on roles and
responsibilities
of Sheffield CTRU
and Study Chief
Investigators**

INTRODUCTION

Trials are complex, challenging and expensive and many trials fail to complete. The National Institute for Health Research (NIHR) Clinical Trial Units (CTUs) Network Executive Committee have recognised that good communication between CTUs and their collaborating investigators is crucial to successful implementation of trials. This includes a clear understanding of roles, responsibilities and expectations early on in the collaboration. This document is based on the NIHR CTU Network Efficient Trial Conduct CI Agreement.



The purpose of this document is to aid discussion and agreement about the roles and responsibilities of the parties involved in the design and implementation of studies undertaken in collaboration with Sheffield CTRU. It aims to set out what clinical investigators can expect of Sheffield CTRU and which responsibilities lie with the chief investigator (CI). It is not intended to include a comprehensive list of all the tasks that will be undertaken during the course of design and implementation of a trial but covers the key areas. There are some responsibilities outlined below that may not be applicable to all trials.

OVERVIEW

Role of

Clinical Trials Units (CTUs)

CTUs are specialist units that have been set up with a specific remit to design, conduct, analyse and publish clinical trials and other well-designed studies. CTUs which have been awarded UK Clinical Research Collaboration (UKCRC) registration are required to provide evidence to an international panel of experts of their capability to centrally coordinate multi-centre clinical trials and that they have established robust systems to ensure conduct and delivery of clinical trials to the highest quality standards. It is essential that the CTU is supported by the study CI to conduct activities in accordance with the CTU standard operating procedures (SOPs). There are many tasks which the CTU is unable to take responsibility for (e.g. patient safety and clinical intervention content expertise) and in order to meet the regulatory standards close working between the CI and the CTU throughout the trial is essential.



Roles and responsibilities of Sheffield CTRU

The CTRU roles and responsibilities include:-

- support for trial design and identifying appropriate methodological collaborators
- co-ordination of preparation and submission of the funding application
- co-ordination of the study implementation post award
- support to ensure the scientific integrity of the trial throughout implementation
- support to ensure the trial is undertaken in accordance with regulatory standards

Roles and responsibilities of the Chief Investigator

The CI's roles and responsibilities include:-

- preparation and submission of the research funding application.
- delivery of the study in accordance with the study timelines and budget as set out in the research protocol.
- clinical oversight and maintenance of the clinical integrity of the trial.
- accountability to the funder to deliver the project in accordance with the terms and conditions of the award.
- delivery of the primary publication of the work in collaboration with the CTRU and collaborating investigators.

Communication

It is important to recognise that regular and substantial communication will be needed between the CTRU and the CI. At times urgent responses will be required from the CI. The CTRU will work with the CI to agree mutually agreeable processes for communication such as using email headings to identify urgent request (e.g. FOR ACTION) and / or weekly implementation team meetings.

Some decisions, particularly related to CTIMPs (Clinical Trial of Investigational Product or drug trial), will need to be communicated by e-mail to ensure a documented trail. In study set up and during challenging periods communication may need to be weekly and the response times to queries may need to be within 2 days (e.g. clinical safety issues and response to funder).

CTRU will be expected to:

- nominate a lead person (CTRU Lead) who will have the expertise and experience to design and oversee the implementation of clinical trials.
- identify a second member of the CTRU senior team who will provide support should the Lead not be able to do so (e.g. in periods of extended absence).
- take responsibility for advising the CI throughout the study design and implementation on scientific, regulatory and practical issues.

CI's will be expected to:

- nominate one or two members of the study team to be able to make decisions on their behalf in case of absence. Separate nominees may be required for different types of decisions e.g. regarding clinical/patient safety, trial processes, negotiations with site investigators.
- be available to communicate with the Sponsor, the funder, the Research Ethics Committee (REC) and other review bodies during the application process and the whole duration of study implementation.
- agree regular times to be available to talk with the study teams as often as weekly at times.
- be available to answer as-hoc informal queries as when they arise.

A typical trial lifecycle:

GRANT DEVELOPMENT & SUBMISSION

PROTOCOL & TRIAL DEVELOPMENT

Protocol Development

Case Report form (CRF) &
Database design

STUDY IMPLEMENTATION

Study Management

Study Governance

Risk Assessment

Safety/Pharmacovigilance

REPORTING AND PUBLICATION

End of study report to
funders

Publication (final study
report and other articles)



Grant Development and Submission

Timelines:

Ideally, the CTRU should be approached at the point at which it is decided that a grant application will be made; at a bare minimum this should be no later than 6 weeks prior to the grant submission deadline

CTRU will:

- ensure the collaboration process is efficiently managed and allow sufficient time to support the CI in the development of the grant funding application.
- provide the CI with support to enable them to submit a complete and competitive grant application including but not limited to, advice on study design, sample size, statistical design, project planning, research costs, regulatory and governance issues and review of the financial application.
- help to identify collaborators with appropriate methodological expertise e.g. qualitative, health economics evaluation and modelling and systematic reviewing.
- explore with the CI and collaborating sites the feasibility of recruitment projections
- explore with the CI and collaborating sites the feasibility of the proposed effect sizes.
- work with local Clinical Research Network (CRN) and NHS partners to determine the research, service support and excess treatment costs associated with the project.
- provide advice and guidance in the costing model for the study
- advise the CI on the cost levels and models likely to be acceptable to the funder.
- prompt discussion of intellectual credit and contributions.

CI's will:

- work with the CTRU to develop the grant application at all stages (outline/full/single stage) and allow sufficient time for collaborators to make a meaningful academic contribution.
- discuss and reach agreements on co-applicants with CTRU before inviting investigators to the team.
- take the lead on writing the grant application.
- provide input to the clinical aspects of the sample size calculation.
- answer costing queries relating to the patient pathway to ensure proper cost attribution.
- manage expectations of co-applicants on what can be included to ensure the proposal is not prohibitively complicated, ambitious or expensive.
- include Senior CTRU staff as co-applicants as appropriate.
- discuss with the CTRU any planned substantial change in the study design/conduct prior to grant submission.
- provide a final copy of the grant submission to CTRU as soon after submission as possible.
- notify the CTRU of the funding decision as soon as possible.

PROTOCOL AND CRF DEVELOPMENT

Protocol development

CTRU will:

- appoint and supervise study staff such as study manager, research assistants and statisticians
- provide the CI with an initial draft of the trial protocol (based on CTRU Protocol template document).
- co-ordinate the multidisciplinary input from a team of experts in the required fields from both within and external to the CTRU.
- ensure the CTRU and Sponsor trial team contribute to the relevant sections of the protocol to support the CI in the writing of the protocol (e.g. statistics, pharmacovigilance, pharmacy etc.).
- manage the protocol review process.

CI's will:

- work on the initial draft of the clinical trial protocol providing clinical input and expertise.
- support the review process in order to finalise the clinical trial protocol.
- ensure the protocol has undergone scientific and statistical review.
- identify and liaise with the individuals who may be able to provide patient and public involvement (PPI).

Case Report Form (CRF) and database design

CTRU will:

- manage the CRF drafting process in parallel with the protocol drafting.
- create a final version of the CRF using the CTU approved template/process and update this as required during the course of the trial.
- ensure the completion of a Data Management Plan in line with CTU SOPs.
- facilitate statistical review of CRFs.
- co-ordinate creation of a validated study database.
- co-ordinate creation of all IT support systems ensuring they are appropriately validated.

CI's will:

- provide input, review and approve the CRFs prior to the trial opening, ensuring that all data is captured as detailed in the protocol to answer the trial endpoints.
- provide clinical input during the CRF drafting process and any amendments required throughout the study.



Statistical Analysis Plan

CTRU will:

- appoint an appropriate statistician to draft the statistical analysis plan.
- provide the CI and research team with an initial draft of the statistical analysis plan (which follows the CTRU SOP requirements).
- co-ordinate the multidisciplinary input into the required analysis.
- ensure required review of statistical analysis plan is completed (including internal senior review and external review i.e. Trial Steering Committee (TSC) as required).

CI's will:

- review and agree the plan for the statistical analysis plan including clinical input where required.
- support the review process in order to finalise the statistical analysis plan.



STUDY IMPLEMENTATION

Study management -

The CTRU will take the lead in study management and liaison with all co-applicants to deliver the study within time and budget..

CTRU will:

- liaise with potential centres, identifying and initiating participating centres and maintaining good communication with each centre.
- produce a study website.
- set up the trial and obtain relevant permissions (ethics approval, MHRA approval etc.).
- recruit clinical sites in order to identify and recruit eligible trial patients and allocate a trial entry number and treatment to trial patients.
- co-ordinate and manage essential trial documents and patient data collected from participating clinical sites.

- undertake data monitoring centrally and at sites if appropriate.
- conduct interim and final analyses.
- prepare reports during the study (e.g. for funding bodies, NRES, MHRA).

CI's will:

- oversee or liaise with CTRU staff on all tasks to ensure mutual understanding and agreement of all study processes; to add clinical knowledge/perspective; and to be available to make final decisions throughout the trial.

Study Governance

CTRU will:

- organise and administer Trial Management Group (TMG), Data Monitoring Committee(DMC), and Trial Steering Committee (TSC) meetings.
- advise on suitable statisticians to sit on oversight committees.
- ensure that a senior applicant from the CTRU (e.g. CTRU Lead or Senior Statistician) will be present at all independent oversight committees meetings e.g. TSCs and DMEC.

- prepare trial progress, data management, clinical safety and statistical reports for the governance committees.

CI's will:

- attend all TSCs and DMECs (except in emergencies and sickness)
- attend all TMGs

It is important that less senior staff such as trial managers and study statisticians do not attend TSCs and DMECs unsupported. With the agreement of the CI, the CTRU Lead and Senior statistician may not need to attend all the TMGs if the trial is progressing without problems and both the trial manager and statistician can attend.

STUDY IMPLEMENTATION

Risk Assessment -

The CTRU and CI are jointly responsible for the trial risk assessment. The risk assessment requires a co-ordinated multidisciplinary approach across the trial team.

CTRU will:

- generate a risk assessment using the CTRU template
- co-ordinate the input from a team of experts in the required fields from both within and external to the CTRU.

CI's will:

- provide clinical input into the risk assessment.
- conduct a final review and approve the risk assessment.



STUDY IMPLEMENTATION

Safety/Pharmacovigilance

CTRU will:

- liaise with the sponsor, CI and pharmacy with respect to the identification and approval of appropriate Reference Safety Information (RSI) for all Investigational Medicinal Products (IMPS) for the trial, this is only relevant to Clinical Trials of Investigational Medicinal Products (CTIMPs).
- liaise with the sponsor and CI regarding safety reporting requirement including, timeframes, excluded events, coding systems etc.
- send reports/emails of all new SAE's to the CI for medical oversight.
- communicate information regarding potential Suspected Unexpected Serious Adverse Reactions (SUSARS)/safety events to the CI.
- provide current approved RSI for IMPS to the CI for advice on the clinical management of trial participants and consideration of expectedness.
- prepare Development Safety Update Reports (DSURs).

CI's will:

- help with the identification of appropriate RSI for all IMPS in preparation for submission to the MHRA (CTIMP ONLY).
- ensure the risks and side effects listed in the patient information sheet are consistent with the RSI for all IMPS (CTIMPS ONLY).
- with input from the trial statistician and any oversight committees review all new SAEs for the trial in an agreed time-scale in order to ensure CI oversight of safety reporting and if any unexpected, untoward safety issues or unanticipated patterns of SAE reporting are identified, the CI will alert the Project Manager immediately.
- review of SAEs for causality and expectedness.
- answer any safety related queries and identify SUSARs.
- review safety alerts.
- keep up to date with the literature to ensure the team are aware of the relevant clinical developments and safety information
- give a clinical opinion on any changes to the trial risk-benefit assessment and the clinical management of patients following the update of RSI and completion of DSUR for IMPS and advise of any changes required to the Patient Information Sheet (PIS), management of the trial and protocol.
- complete RSI review on receipt of update.



REPORTING AND PUBLICATION

End of Study Report to Funder -

The writing, approving and distribution of the End of Study report is a team responsibility and although the trials unit can facilitate the activity it needs input from all parties

CTRU will:

- prepare and submit end of trial notification to applicable bodies.
- upload a summary of results to EudraCT and/or the registry on which the trial was originally registered within 2 years of the last data collection time point.
- co-ordinate the writing of the End of Study report(s) for submission to applicable bodies liaising with all collaborators and investigators as appropriate.
- produce an outline for the report in accordance with the CTRU Report Template and draft specific sections including the contents page, methods, results, glossary, index, protocol revisions.
- take responsibility for formatting the report.
- reach agreement with the CI and collaborators on responsibility for all remaining sections e.g. literature review, intervention fidelity, discussion.

Response to reviewers comments:

- response to reviewers comments on the report related to methodological aspects (e.g. presentation and analysis of quantitative and qualitative data)
- aim to provide support for co-ordination of study team contributions to the comments but it should be noted that at this time the study funding will have ended and study management and administrative staff (who are all grant funded) may no longer be available.

CI's will:

- author sections of the End of Study report as agreed with the CTRU, typically the abstract, contextualising/interpretations of results, discussion, conclusions, extended scientific summary and any specialist areas within the CI's domain (e.g. intervention fidelity).
- edit, review, approve and sign off end of trial reports.
- ensure that the study team, at minimum the CTRU Study Lead and Senior statistician, are aware of drafts and the final submission in a timely manner prior to submission.

Response to reviewers comments:

- take responsibility for the response to the reviewers comments and amendments to the report.
- ensure that the study team, at minimum the CTRU Study Lead and Senior statistician, are aware of drafts and the final submission in a timely manner prior to submission.



Publication (Final Study Manuscript plus other Articles)

CTRU will:

- as early as possible in the study, produce a publication plan in agreement with the CI.
- assist in the manuscript preparation in association with the CI
- help to identify the target journal (s) for publication if required.
- prepare appropriate and relevant summary tables and figures for presentation of results.
- provide a final statistical report and statistical input into the manuscript in line with the Statistical Analysis Plan (SAP).
- it should again be noted that at the time of paper writing the study funding may have ended and study management, administrative staff and statisticians (who are all grant funded) may no longer be available.
- **CTRU often has insufficient statistical resource to conduct post hoc analyses which have not been previously agreed in the SAP.**

CI's will:

- initiate and lead on the preparation of the final study manuscript process.
- identify target journal(s) for publication.
- review and approve the final statistical report.
- identify who will be involved in the writing up of the final study manuscript.
- produce the final study manuscript (ready for submission).
- ensure that the study team, at minimum the CTRU Study Lead and Senior statistician, are aware of drafts and final submission in a timely manner prior to submission.
- be aware that any changes to the manuscript will require review by the study statistician for Quality Assurance purposes prior to submission or re-submission.

CTRU STAFF DEVELOPMENT

It is important to be aware that CTRU staff will be expected to spend some of their time in career development activities during study implementation time. Staff development is essential to delivery of high quality research and retention of experienced staff. This is likely to include some activities related to teaching or progression of their own research.

CTRU staff (including Trial Managers, Statisticians and other affiliated research staff) should be given the opportunity to input into a least two main publications per study, either as primary author or co-author..

