York Foundation Trust R&D Unit
Standard Operating Procedure
R&D/S02

Application to the Trust for Sponsorship of a CTIMP

IT IS THE RESPONSIBILITY OF ALL USERS OF THIS SOP TO ENSURE THAT THE CORRECT VERSION IS BEING USED

All staff should regularly check the R&D Unit's website and/or Q-Pulse for information relating to the implementation of new or revised versions. Staff must ensure that they are adequately trained in the new procedure and must make sure that all copies of superseded versions are promptly withdrawn from use unless notified otherwise by the SOP Controller.

The definitive versions of all R&D Unit SOPs appear online. If you are reading this in printed form check that the version number and date below is the most recent one as shown on the R&D Unit website: www.northyorksresearch.nhs.uk/sops.html and/or Q-Pulse

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Approved by:	Name/Position:	Lydia Harris, Head of R&D
	Signature:	Signed copy held by R&D Unit
	Date:	12th July 2017
	Name/Position:	Sarah Sheath, SOP Controller
	Signature:	Signed copy held by R&D Unit
	Date:	12th July 2017

As a minimum, this SOP will normally be reviewed every 3 years unless changes to the legislation require otherwise

Version History Log

This area should detail the version history for this document. It should detail the key elements of the changes to the versions.

Version	Date Implemented	Details of significant changes
1.0	13th January 2009	
2.0	21st October 2009	Changes to review dates. Change to SOP number. Inclusion of notification of successful feasibility review to Pharmacy. Put into revised template. Inclusion of green and amber light process.
3.0	1st July 2010	Modified to include registration of trial on eSUSAR database. Template letters added.
4.0	28th March 2012	General update. Change to terminology 'permission to recruit'. Removal of need to submit draft SSI Forms and incorporation of RSS assessment. Change of SOP Controller
5.0	28th October 2013	Removal of references to the North and East Yorkshire Alliance. Shortening of introduction. Removal of requirement to send to Trust R&D lead as now only relevant to York and R&D lead is a member of the R&D Group.
6.0	11th January 2017	Updated to include HRA and confirmation of capacity and capability
7.0	14th August 2017	

Contents

1 Introduction, Background and Purpose

When an organisation agrees to sponsor a CTIMP it takes on a major responsibility. Because this is such a serious undertaking, considerable time and effort must be devoted to setting up a CTIMP. The protocol and all documentation and procedures associated with it must be developed in detail; monitoring must be arranged and the monitor involved in the trial initiation process; all investigators must be trained; there must be sufficient financial and human resources available for safe and effective conduct of the trial. Investigator teams will need to work with the R&D Unit on all these matters.

An application to the Trust to sponsor a CTIMP is, therefore, considered in stages:

1. Feasibility Review

   The proposed Chief Investigator (CI) submits to the R&D Group an outline protocol, a basic funding plan and details of the investigator team – qualifications, experience, research training, other current research projects, proposed responsibilities in the trial and time available to carry them out. The Group will decide whether the proposal has potential scientific merit, is practicable, is likely to be adequately resourced, and whether the investigator team has the capacity to carry it out safely and effectively.

2. Full Trial Development

   If the Group agrees that the basic feasibility requirements have been met the investigator team will work with the R&D Unit to produce a detailed CTIMP – appropriate protocol, data collection tools and procedures designed to fit with the sponsor's standard operating procedures, investigational medicinal product handling plans, detailed costings and so on. All this will be submitted for independent peer and statistical review before it is submitted again to the R&D Group for approval of sponsorship "in principle".

3. Final Approval

   If the Group agrees sponsorship in principle, the investigators will apply for the Clinical Trial Authorisation (or 'notification' for certain types of trial) and HRA approval. If plans for the trial are changed as a result of this process the trial documentation will return to the R&D Group for further consideration. If no significant changes are made then upon receipt of written confirmation of approval by the MHRA and HRA, final sponsorship approval will be issued.

Funding

Because funding arrangements vary considerably it is recognised that it may be necessary for some flexibility to make this process work in conjunction with outline or full applications for grants and conclusion of grant contracts.

ABBREVIATIONS USED IN THIS DOCUMENT	
CI	Chief Investigator
CRF	Case Record File
CTA	Clinical Trial Authorisation
CTIMP	Clinical trial of an investigational medicinal product
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice (standards in clinical trials)
GMP	Good Manufacturing Practice (standards for IMPs)
HRA	Health Research Authority
IB	Investigator Brochure
ICH-GCP	International Conference on Harmonisation - Good Clinical Practice (in clinical trials)
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IRAS	Integrated Research Application System
MHRA	Medicines and Healthcare Products Regulatory Agency
PI	Principal Investigator (at study site)
PIS	Participant Information Sheet
QA	Quality Assurance
R&D Group	York Teaching Hospital NHS Foundation Trust R&D Group
R&D Unit	York Foundation Trust R&D Unit
REC	Research Ethics Committee
the Regulations	Regulations under the Medicines for Human Use (Clinical Trials) Regulations 2004 and related Statutory Instruments.
SmPC	Summary of Product Characteristics
SSI	Site-Specific Information

2 Who Should Use This SOP

Investigators seeking sponsorship of a clinical trial of an investigational medicinal product (CTIMP) by the Trust should use this SOP.

3 When this SOP Should be Used

This procedure applies when an investigator seeks sponsorship of a clinical trial of an investigational medicinal product (CTIMP) by the Trust.

4 Procedure(s)

Is the study a CTIMP?

To find out whether your trial is a CTIMP, seek advice from the R&D Unit to help you in using the MHRA algorithm.

If, after using the algorithm, you are still unsure whether or not the trial is covered by the Regulations send an e-mail to the MHRA Clinical Trial Helpline (clintrialhelpline@mhra.gsi.gov.uk) marked **'**scope-protocol review' in the subject line and request an opinion on the status of the trial. A copy of the draft protocol should be provided with the request – this will probably not be in its final form but should be sufficiently detailed to enable the MHRA to see what you intend to do. You must ensure that all correspondence with the MHRA is retained.

If your study is a CTIMP, confirmation that the Trust will act as sponsor will only be obtained through the following application process.

4.1 Stage 1: Feasibility Review (see Appendix A)

4.1.1 Contact R&D Unit

It is important to contact the R&D Unit at this early stage if you have not already done so. The R&D Unit will issue you with an R&D reference number which should always be used when corresponding regarding the trial or when making a submission.

4.1.2 Prepare documentation for Feasibility Review

- At this stage the draft protocol should contain a brief literature review and justification for the proposed research, and should describe clearly the essential elements of the trial. This document can be used for preliminary discussions with potential trial partners, the MHRA or the potential sponsor. It may be sufficient for an outline grant funding application.
- CVs for Chief Investigator (CI) and all other investigators in the team – use Health Research Authority (HRA) guidance for this to avoid having to duplicate work later. Include details of GCP training undertaken, with dates.
- Draft Patient Information Sheet (PIS) – use HRA guidance.
- Draft consent form – use HRA guidance.
- Completed Feasibility Application Form (refer to Section 5)

4.1.3 Submit documentation for internal review

The CI should submit documentation to research.governance@york.nhs.uk marked ***CTIMP feasibility review*** in the subject heading. The R&D Unit will perform an initial review of the application within 10 working days and complete the Feasibility Checklist (refer to Section 5) which will also be submitted for consideration by the R&D Group (section 4.1.4).

4.1.4 R&D Group review

The application documents, Feasibility Checklist and any accompanying report from the R&D Unit will be submitted to the next available R&D Group meeting by the R&D Unit. The CI may be invited to attend the meeting to discuss the proposed study and answer any questions.

The Group may decide:

- That the proposed study is not feasible in its current form and will not be sponsored by the Trust concerned;
- That if the investigators wish to do further preliminary work on areas specified by the Group, the Group will be prepared to consider a re-submission for Feasibility Review.
- That the proposed study is feasible and should go forward to the Full Study Development stage.

4.1.5 Communication of result

The Group's decision will be communicated to the CI in writing as soon as possible after the meeting (normally within 7 working days). A copy of this communication will be sent to the Trust Pharmacy Trial team and also to any other involved departments for early information.

4.2 Stage 2: Full Trial Development (see Appendix B)

When a trial goes forward to this second stage a request is made for sponsorship in principle. This is important as some funding bodies require that sponsorship be agreed at least in principle prior to accepting a funding application.

The sponsor of a clinical trial must satisfy itself that the trial meets all relevant standards and ensure that arrangements are put and kept in place for adequate management, monitoring and reporting. Investigators are asked to note that it is quite normal to take several weeks or even months to refine the plans and prepare the detailed documentation required at this stage. Arrangements must be made for matters such as randomisation of participants, manufacture, packaging, supply, storage and dispensing of IMP (including placebo substances) and provision of any laboratory services. All this is essential because the proposed sponsor must make a fully-informed decision on whether it is able to meet the requirements of the study sponsor as defined in the Regulations, and detailed contracts will have to be negotiated with all involved parties. Investigators must, therefore, be prepared to spend as much time as is necessary working up the protocol and other documentation in collaboration with the R&D Unit, incorporating expert statistics and study design advice, drafting a monitoring plan and developing all the relationships that will be essential for the trial

At the end of this period you should have a set of documents that are ready for the "sponsorship in principle" application to the R&D Group.

4.2.1 Submit documentation for "sponsorship in principle" application

1. Protocol using the HRA recommended template adhering to the guidelines within the template;
2. PIS;
3. Consent form;

4. CRF;
5. Other key clinical documents (e.g. diary cards/questionnaires);
6. Drafts of any communication with patients, participants, GPs or recruitment advertisements – use HRA guidance;
7. Clinical Trial Risk Assessment, using sponsor-approved template (see Section 5);
8. Draft Schedule of Events
9. Draft Statement of Activities
10. Any relevant draft contracts or confidentiality agreements that investigators have received from other parties;
11. Copy of Summary of Product Characteristics (SmPC), Investigator Brochure (IB) and/or Investigational Medicinal Product Dossier (IMPD);
12. Investigator team CVs (which must document GCP training);

The submission should be sent to research.governance@york.nhs.uk with the subject heading ***CTIMP Sponsorship in principle application.***

4.2.2 Internal review of Sponsorship in Principle application

The R&D Unit will perform a review of the application and initial comments will be sent to the CI within 10 working days for response/protocol modification as required. The investigator team may respond in writing and/or submit revised documentation for consideration.

The R&D Unit will develop a draft monitoring plan for the trial in line with the R&D Unit monitoring SOP (refer to Section 5) and this will be included in the paperwork for consideration by the R&D Group.

4.2.3 External review of Sponsorship in Principle application

Following internal review and response from the CI, the application should be submitted for:

- External peer review
- Statistical review
- Pharmacy review
- Financial review
- Review by any other involved departments (e.g. Laboratory or Radiology)

Copies of the reviews will be sent to the CI as soon as possible after receipt by the R&D Unit. The aim is to do this within 4 weeks but investigators will appreciate that we can only request external reviewers to meet our deadlines and they may be unable to do so. The CI will have the opportunity to respond to the reviewers' comments. Once a response from the CI has been received or confirmation of no response is given, the complete application will be booked into the next available slot at an R&D Group meeting.

4.2.4 R&D Group review of Sponsorship in Principle application

The R&D Group will consider the complete application incorporating all of the submitted documentation, the peer reviewers comments, risk assessment and monitoring plan, and make a decision as to whether the Trust is, in principle, able to act as sponsor for the trial. The CI will be invited to attend the relevant part of the meeting. The Group's decision will be communicated to the CI in writing, usually within 7 working days. A copy of this communication will be sent to the Trust Pharmacy and other involved departments (where appropriate).

The Group's decision that the Trust is prepared to accept sponsorship in principle will allow the CI to proceed with applications to funding bodies, REC, HRA and the MHRA.

It is important to remember that FINAL sponsorship approval and confirmation of Capacity and Capability are both required before the trial can commence.

4.3 Stage 3: Final Approval (see Appendix C)

4.3.1 Regulatory approval

Once sponsorship in principle has been granted, the investigator may proceed with obtaining (i) a EudraCT number, (ii) ISRCTN registration, (iii) REC approval, (iv) HRA approval and (v) Clinical Trial Authorisation from the MHRA, or notification for low risk trials. Advice on all these applications can be given by the R&D Unit.

Before making regulatory submissions the investigator must incorporate all protocol and related document amendments, as specified during the sponsor review process. The necessary signatures on behalf of the Sponsor can then be provided by the Head of R&D or Research Adviser. Copies of the applications should be provided to the R&D Unit, for retention on behalf of the Sponsor.

4.3.2 Final Sponsorship Approval

Once REC, HRA and MHRA approval has been received (or in the case of Type A trials, acknowledged) the CI should forward copies of the approvals (or acknowledgement) and any amended documents to the R&D Unit. If significant changes have been required as a result of the regulatory applications, the R&D Unit may return the application to the R&D Group for further consideration. If everything is found to be in order at this stage then FINAL Sponsorship approval will be granted and communicated in writing.

At this stage, the R&D Unit (Research Adviser Lead) will put in place final Sponsor oversight arrangements for the trial, including:

1. registering the trial on the MHRA's eSUSAR website (http://esusar.mhra.gov.uk/).

2. convening a Data Monitoring Committee (where required) and agreeing Terms of Reference.

3. appointing a suitable GCP trained Medical Expert, agreeing their specific role for the trial, and ensuring appropriate trial specific training is undertaken.

4.3.3 Applying for confirmation of Capacity and Capability

It is expected that investigators will have developed strong collaborations with any proposed trial sites during the study development process and that these sites are named on the IRAS Form.

Once Sponsorship is confirmed to be in place an investigator (or delegate) must formally submit the necessary local information packs (refer to HRA website for recommended list of documents) to all site R&D Units so that they can consider and confirm their site's capacity and capability. It would be

expected that the local Trust would open the study first in order to identify any remaining issues that might be required to be resolved prior to rolling out to other sites.

In addition the following must take place in a timely manner alongside information pack submission:

- *Trial Initiation Session(s):* The CI should arrange, in liaison with the appointed trial monitor, trial manager and R&D unit, one or more trial initiation sessions. All investigators should previously have received training in the running of trials to GCP standards. The aim of the initiation session is to provide trial-specific training in the protocol, data recording methods and standard operating procedures, to go through the contents of the TMF/ISF, to answer queries and address any inconsistencies. It should also give the Monitor an opportunity to clarify the expectations that will underlie monitoring and to highlight any potential pitfalls s/he may identify. Following the trial initiation the Monitor or Trial Manager will submit a brief written report to the Sponsor confirming whether the Site has been successfully initiated. In the event that the Sponsor does not consider a site to have been successfully initiated then recruitment will be suspended at that site until the issue is resolved.
- *Trial master File/Investigator Site File*: The CI should compile the Trial Master File (TMF), advice and assistance can be sought from the R&D Unit; and, in addition, an Investigator Site File (ISF) for each Investigator Site (NHS Trust) participating in the trial. Refer to the relevant SOPs detailed in Section 5.
- *Final preparations by involved departments:* The CI (or PI at other sites) should liaise with all other departments involved in the trial to ensure that everything is in place for commencement of the study. This will include final arrangements for matters such as randomisation, shipping of IMP to site(s), unblinding arrangements, laboratory services.

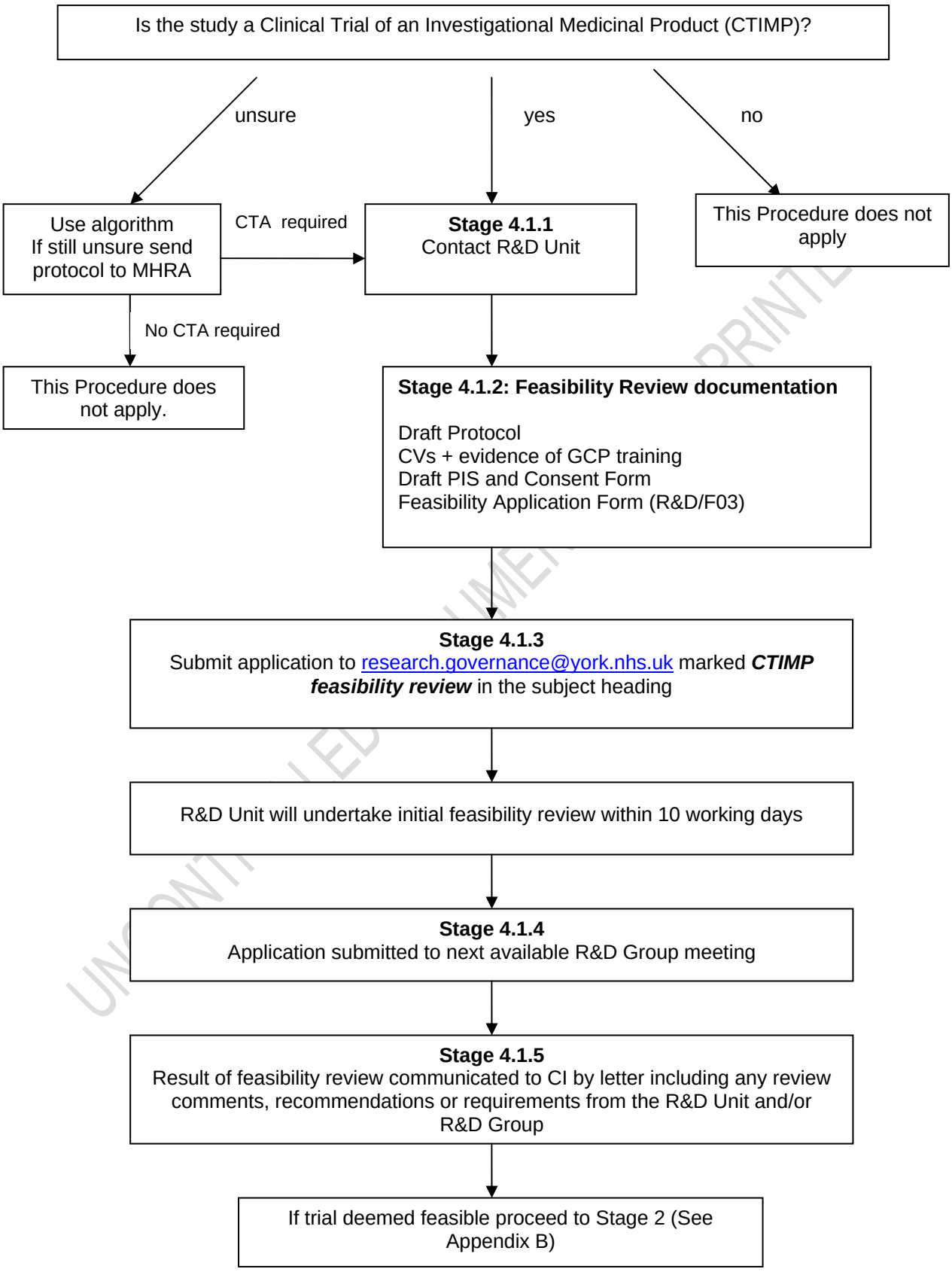
4.3.4 Receiving confirmation of Capacity and Capability

If the R&D Unit is satisfied that all is in order then capacity and capability will be confirmed in writing.

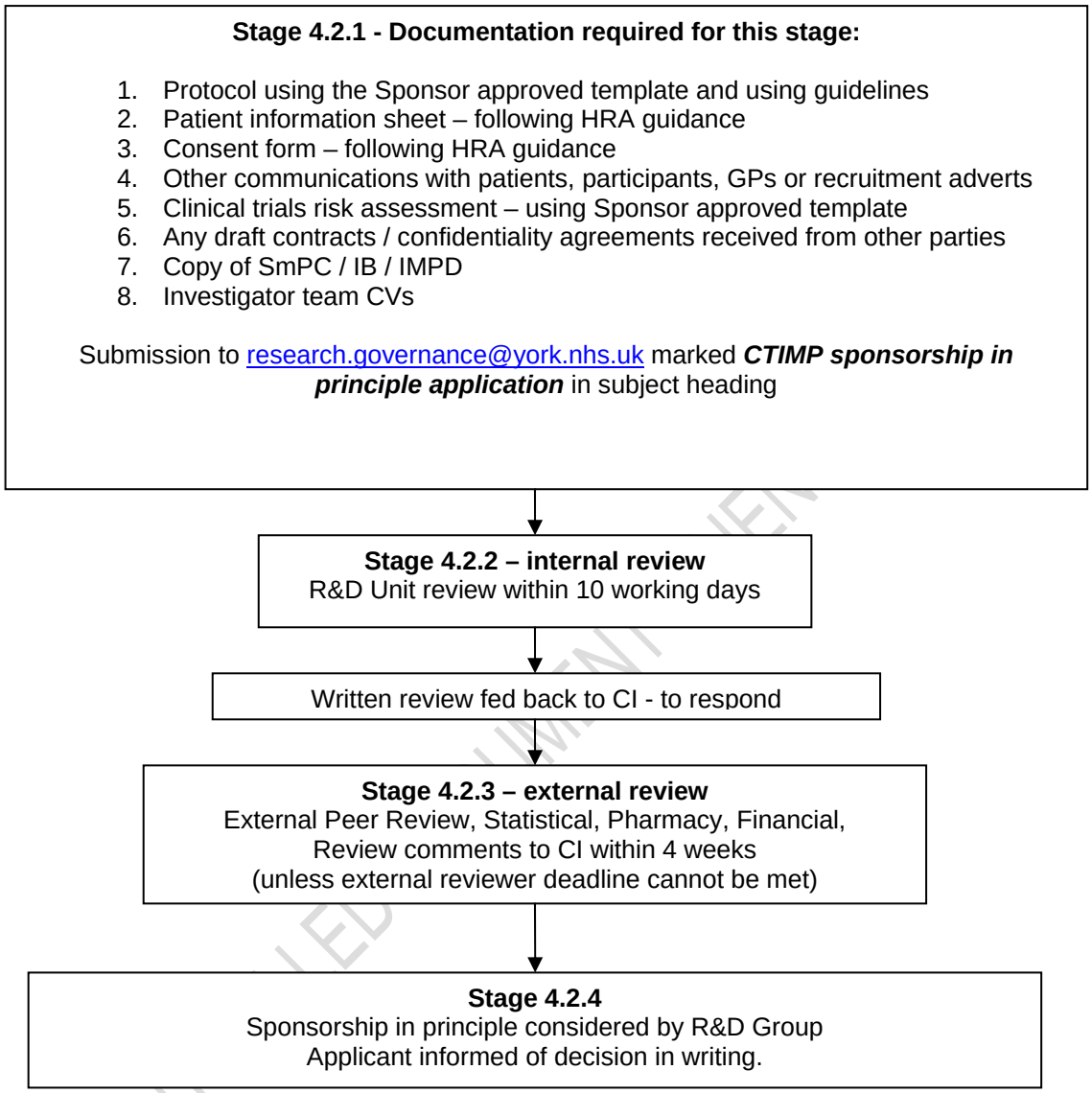
5 Related SOPs and Documents

R&D/F03	Feasibility Application Form
R&D/F04	Feasibility Checklist
R&D/S03	Delegation of Tasks for Trust sponsored CTIMPs
R&D/S08	Monitoring of Trust Sponsored Research Studies
R&D/S09	Set up and management of Research Studies
R&D/S14	Local New Study Set-Up: Capacity and Capability Assessment
R&D/F11	Trial master File/Investigator Site File contents
R&D/S18	Risk Assessment
R&D/T21	Feasibility Review Result Template Letter/Email
R&D/T22	Sponsorship in Principle Letter/Email
R&D/T23	Final Sponsorship Letter/Email

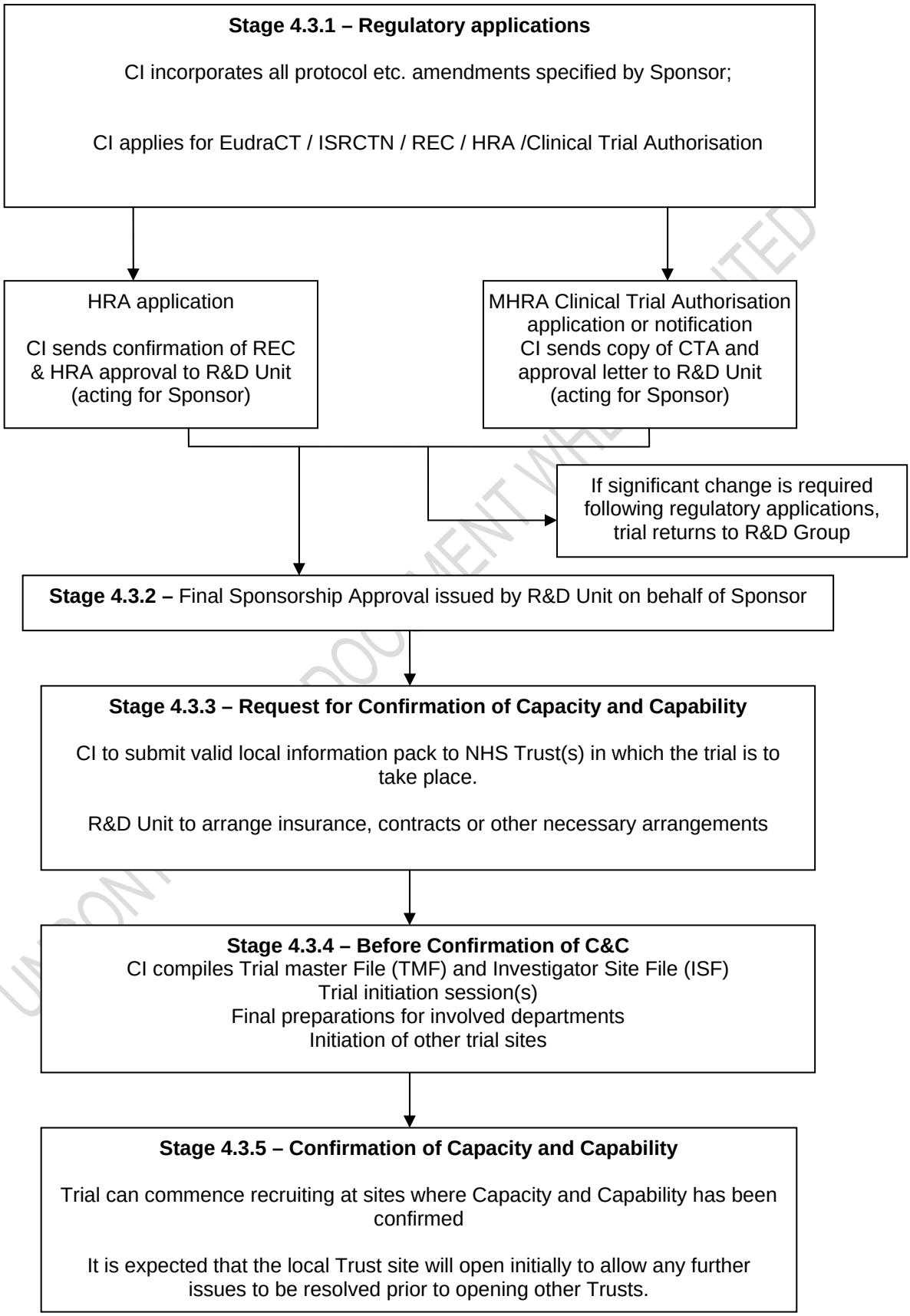
Appendix A


Is the study a Clinical Trial of an Investigational Medicinal Product (CTIMP)?
unsure
yes
no
Use algorithm
If still unsure send protocol to MHRA
CTA required
Stage 4.1.1
Contact R&D Unit
This Procedure does not apply
No CTA required
This Procedure does not apply.
Stage 4.1.2: Feasibility Review documentation
Draft Protocol
CVs + evidence of GCP training
Draft PIS and Consent Form
Feasibility Application Form (R&D/F03)
Stage 4.1.3
Submit application to research.governance@york.nhs.uk marked CTIMP feasibility review in the subject heading
R&D Unit will undertake initial feasibility review within 10 working days
Stage 4.1.4
Application submitted to next available R&D Group meeting
Stage 4.1.5
Result of feasibility review communicated to CI by letter including any review comments, recommendations or requirements from the R&D Unit and/or R&D Group
If trial deemed feasible proceed to Stage 2 (See Appendix B)

Appendix B


Stage 4.2.1 - Documentation required for this stage:
1. Protocol using the Sponsor approved template and using guidelines
2. Patient information sheet – following HRA guidance
3. Consent form – following HRA guidance
4. Other communications with patients, participants, GPs or recruitment adverts
5. Clinical trials risk assessment – using Sponsor approved template
6. Any draft contracts / confidentiality agreements received from other parties
7. Copy of SmPC / IB / IMPD
8. Investigator team CVs
Submission to research.governance@york.nhs.uk marked CTIMP sponsorship in principle application in subject heading
Stage 4.2.2 – internal review
R&D Unit review within 10 working days
Written review fed back to CI - to respond
Stage 4.2.3 – external review
External Peer Review, Statistical, Pharmacy, Financial,
Review comments to CI within 4 weeks
(unless external reviewer deadline cannot be met)
Stage 4.2.4
Sponsorship in principle considered by R&D Group
Applicant informed of decision in writing.

Appendix C


Stage 4.3.1 – Regulatory applications
CI incorporates all protocol etc. amendments specified by Sponsor;
CI applies for EudraCT / ISRCTN / REC / HRA /Clinical Trial Authorisation
HRA application
CI sends confirmation of REC & HRA approval to R&D Unit (acting for Sponsor)
MHRA Clinical Trial Authorisation application or notification
CI sends copy of CTA and approval letter to R&D Unit (acting for Sponsor)
If significant change is required following regulatory applications, trial returns to R&D Group
Stage 4.3.2 – Final Sponsorship Approval issued by R&D Unit on behalf of Sponsor
Stage 4.3.3 – Request for Confirmation of Capacity and Capability
CI to submit valid local information pack to NHS Trust(s) in which the trial is to take place.
R&D Unit to arrange insurance, contracts or other necessary arrangements
Stage 4.3.4 – Before Confirmation of C&C
CI compiles Trial master File (TMF) and Investigator Site File (ISF)
Trial initiation session(s)
Final preparations for involved departments
Initiation of other trial sites
Stage 4.3.5 – Confirmation of Capacity and Capability
Trial can commence recruiting at sites where Capacity and Capability has been confirmed
It is expected that the local Trust site will open initially to allow any further issues to be resolved prior to opening other Trusts.