DIVISION OF RESEARCH AND INNOVATION

Joint Research and Development Office

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Title: **OBTAINING AND MAINTAINING APPROVALS FOR GOSH SPONSORED CTIMPS**	
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	Name	Position
Authored by:	Ilyas Ali	R&D Clinical Trials Manager
Approved by:	Dr Vanshree Patel	R&D Head of Governance, Clinical Trials and Contracts

1. Scope

This SOP covers the procedures to obtain the necessary approvals to conduct a GOSH sponsored Clinical Trial of an Investigational Medicinal Product (CTIMP). The procedures detailed in this SOP are mandatory to all GOSH sponsored CTIMPs trials; This SOP covers the procedure used by the user to request clinical trial authorisation from MHRA and favourable opinion from ethics and any other approval as required.

2. Purpose

The purpose of this SOP is to guide the R&D, investigators and their team conducting clinical trial of medicinal product on how to obtain relevant regulatory authorities approvals for their trials.

3. Definitions/Abbreviations

Regulatory authorities are bodies, which monitor healthcare research to ensure the safety of the population. Each healthcare sector is regulated differently and by more than one body. In the UK, the main regulating bodies are the MHRA and the Ethics Committee, as well as other committees, which may be involved depending on the clinical speciality of the research conducted.

All necessary approvals must be sought prior to commencement of a clinical trial and regular reports must be submitted to the authorities in timely manner.

ARSAC (Administration of Radioactive Substances Advisory Committee)
CAG (Confidentiality Advisory Group)
CESP – Common European Submission Portal
CTA – Clinical Trial Authorisation
CTU – Clinical Trials Unit
GOSH – Great Ormond Street Hospital for Children NHS Foundation Trust
GTAC – (Gene Therapy Advisory Committee)
HRA (Health Research Authority)
IB/SmPC – Investigator Brochure/Summary of Product Characteristic – Document contains clinical information
IMPD – Investigational Medicinal Product Dossier – IMP technical information
IRAS (Integrated Research Application System)
MHRA (Medicines and Healthcare products Regulatory Agency)
MIA (IMP) – Manufacturing Authorisation – This is the licenced unit number where IMP manufacture.
REC (Research Ethics Committee)
RSI – Reference Safety Information
QP – Qualified Person – A person who confirmed product are manufactured as per GMP and suitable for use in clinical trial,

4. Responsibilities

Duties may be delegated but the responsibility always remains with those listed in regulations.

It is the Chief Investigator's (CI) or designated staff's responsibility to obtain all necessary approvals prior to the start of a clinical trial. The R&D office can help in determining whether your study falls under the clinical trials regulations and would therefore require Clinical Trial authorisation. Alternatively you can use the MHRA clinical trial algorithm which can be found here: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/317952/Algothrim.pdf

It is the Sponsor's responsibility to ensure that all necessary approvals are in place throughout the duration of the clinical trial as well as ensuring that the approvals' conditions are adhered to all times.

5. Procedure

The below steps are a mandatory requirement in starting a clinical trial. Each step is detailed below.

5.1 Registering a trial on EudraCT to obtain EudraCT number

EudraCT is a database of all clinical trials. Before any functionality of EudraCT can be used for a given clinical trial, a EudraCT number must be created in order to provide a unique reference for that trial. We will continue to register all CTIMP on EudraCT until MHRA advice otherwise.

- The EudraCT number is unique for your trial, i.e. for one specific clinical trial protocol and NOT for a specific drug.
- If you are conducting the trial at many sites in the UK/Europe/US (i.e. a multi-centre trial) you do **not** need to obtain a different number for each site.

More information on how to register your project and other functionality of EudraCT system can be obtained from the following website, 'how you will need to register first as a user'
https://eudract.ema.europa.eu/results-web/index.xhtml &
https://eudract.ema.europa.eu/help/Default.htm .

Once the project is registered, the user will receive an email confirming EudraCT number which is unique to the trial and used for all correspondence for e.g. CTA application, SUSAR and submission of results.

5.2 Completing IRAS Application

The Integrated Research Application System (IRAS) is a single system for applying for the permissions and approvals for health care research in the UK. This enables you to enter the information about your project once, instead of duplicating information in separate application forms. It uses filters to ensure that the data collected and collated is appropriate to the type of study, consequently the permissions and approvals required and helps you to meet regulatory and governance requirements.

Complete the whole dataset on IRAS and save the application in the format required for submission to MHRA and ethics application. Investigator should complete the MHRA form on the IRAS website.

If you are a new user you will need to create an account. More information on how to create IRAS login and complete application can be obtained from IRAS website: https://www.myresearchproject.org.uk/Signin.aspx

There is also online training available for IRAS on:
https://www.myresearchproject.org.uk/ELearning/index.html
https://www.myresearchproject.org.uk/help/hlpmhramedicines.aspx

The IRAS form is divided into different sections, which need to be answered carefully.

Part	Details

Form Filter	Asks a limited number of key questions about the nature of your research. An application form specific to your project will be created from the answers you give. You need to select your answers carefully.
A	Asks for generic information relevant to all research proposals. Certain questions will be deactivated depending on your answers to the form filter.
B	Is divided into several discrete sections, which refer to particular specialist topics. These appear (or disappear) in response to your answer the form filter.
C	Ask for a list of sites that the study will be conducted at.

5.3 Complete the Applicant's Checklist

You must also complete the online 'Applicant's Checklist' with your IRAS application to ensure that all of the paperwork required to support your application is sent to the REC. You must have all appropriate documents to support your application. The list of required documents is present on the IRAS document checklist and can also be sought from GOSH R&D clinical trials team.

5.4 Submission to Ethics and HRA

Once the IRAS application is complete (IRAS form), authorised by relevant signatories (usually Chief Investigator and sponsor representative) and you are ready with your study documents the ethics review can be booked online on IRAS website. Login to your IRAS form and go to e-submission tab to book the slot. If you require any assistance with booking contact on 0207 104 8008 between 9am and 4.30pm. You will have to submit the signed IRAS form and study document electronically on the same day. Once the REC Committee is booked, you can add REC details in the designated section in the IRAS form. Do not change any other section as it will invalidate the form.

Further information on selection of ethics committee, booking and HRA approvals can be found at below links:
https://www.hra.nhs.uk/approvals-amendments/
https://www.hra.nhs.uk/about-us/committees-and-services/central-booking-service/

5.4.1 – What happens next

The REC committee will validate the application and may request some additional information prior to validation. Once the validation is complete REC will send a validation letter advising of meeting date and time. It is recommended that investigator should attend this meeting. The REC may seek some clarification during this meeting.

In the meantime HRA will issue Initial Assessment Letter. The sponsor/investigator should send all documents and initial assessment letter to the site(s) to ensure the site start their review process for capacity and capability confirmation.

If GOSH is the sponsor of your clinical trial, you should send a copy of your response to R&D office quoting R&D Number to research.governance@gosh.nhs.uk

After the meeting, if REC is satisfied with the project and documentation, they will confirm their formal decision as a favourable opinion or provisional approval with additional information to be provided within a maximum of 10 working days of the meeting. Please read the letter carefully before you respond. Usually REC will issue their favourable opinion within 60 days from the validation letter.

Once MHRA, REC and any other relevant approvals are in place, HRA will issue their approval and this should be forwarded to each site.

5.5 Submission to MHRA

The IRAS application mentioned above includes various forms to complete in order to submit to the relevant authorities according to the project requirement. Complete the MHRA clinical trial application on the IRAS website. EudraCT form is no longer in use.

The MHRA form is divided into different sections which need to be answered carefully.

Filter	
A	Trial Information
B	Identification of the sponsor responsible for the request
C	Application Identification
D	Information on each IMP
E	Design of trial
F	Population of trial subjects
G	Proposed Trial Sites/Investigators in the Member State
H	Competent Authority/Ethics Committee
I	Signature
J	Checklist

Once the MHRA application form on IRAS is complete and authorised by relevant signatories, download the PDF and XML file.

There are also other supporting documents required for MHRA submission and the information on these can be found on the link below or seek advice from GOSH R&D clinical trials team.
https://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk

The cover letter should include some key points which you would like MHRA to consider The cover letter should state minimum:

- Date and Trial information
- the reference to RSI (reference safety information) for e.g. which section of IB or Smpc
- Exemption to labelling if not required in your trial
- Any other key area you want to highlight for assessor. This will help assessor.
- Purchase Order number – if available but not mandatory.

When all documents are complete and ready, submit all documents to MHRA via MHRA submission portal using your user details if already registered.

GOSH R&D is registered on the MHRA submission portal as Sponsor organisation. It is strongly advisable not to use personal individual login details to submit GOSH sponsored trials. All new users should contact the Clinical Trial Team at R&D office obtain their user ID. Users will need GOSH email address to register on the MHRA portal. New users can refer to MHRA submission guidelines from Clinical Trial team for submission process.
https://mhrabpm.appiancloud.com/suite/sites/MHRA_Submissions

For hosted CTIMPs where R&D is supporting the submission
The sponsor organisation should add you as an external user under their company portfolio and then you can submit application under their portfolio using your login details. However it is acceptable if GOSH can use their own ID for submission.

For GOSH sponsored CTIMPS where external CTU/third party involved in submission:
The person involved in the submission should be added under GOSH portfolio, same as GOSH adds their organisation user. However the person submitting the application must be registered under their company portfolio and that company must be registered in MHRA submission portal.

5.5.1 – What happens next

The application will be validated on receipt and acknowledgement letter will be emailed to person submitting and/or sponsor. If the application is valid assessment will begin and it normally takes 30 days (90 days for Gene Therapy). If there are any deficiencies, the applicant will be notified. For the purpose of calculation the day of receipt of valid application by MHRA CTU is day 0. Applicant/sponsor should receive approval letter within 35 days (95 days for Gene Therapy), if you don't hear from them with these time frames then contact MHRA.

The applicant listed in section C1 of annex form 1 (CTA application) or D1 of annex form 2 (Amendment application) will receive an invoice to allow you to make payment once the application is validated. Once the invoice is received forward to

finance department for payment. Penalty fee may be incurred for non-payment and may lead to suspension of authorisation. If you require any further information contact sales.invoices@mhra.gov.uk

Possible outcomes:

There are two possible outcomes:

- Acceptance with or without conditions
- Grounds of non-acceptance

The CI/PI must read the approval letter carefully and address any remarks / comments in collaboration with the sponsor.

If there are any grounds for non-acceptance, follow the instructions on the letter. The amended request is assessed within total 60 days from receipt of initial application (90 days for gene therapy products). The amended request has two possible outcomes:

- Notice of acceptance of amended request
- Ground of non-acceptance

Once you have MHRA approval, send this to the HRA approval team so that they can issue HRA approval on a condition if the study has already REC approval.

5.6 Changes during trial/Compliance to authorisation

a) During the conduct of the trial any significant changes to the clinical trial application (for e.g. protocol update, IB update etc.) should be done via an amendment to MHRA/REC depending on the changes. This can be done via substantial amendment only. MHRA doesn't accept non-substantial amendment however they expect that non-substantial amendment is reviewed and documented on the Amendment log. Further information on amendments available in the amendment SOP GOSH/ICH/SOP/R /005

b) All non-substantial amendment must be approved by HRA except IMPD changes.

c) Any serious breach must be reported to MHRA/REC within 7 days of being made aware

d) Any SUSARs must be reported to competent authority/REC within 7 days or 15 days depending on the criteria. For additional information follow Pharmacovigilance and Safety Reporting SOP GOSH/ICH/SOP/R/007

The MHRA may suspend or terminate a clinical trial where they feel the conditions for authorisation are not being met. The investigator/sponsor must notify competent authority within 90 days of conclusion of trial.

It is now a requirement for all CTIMPs conducted in UK to post their final results on Public database for e.g. Clinicaltrial.gov or ISRCTN with six months for paediatric trials

and one year for other studies. The Sponsor can delegate this duty to the Investigator or their delegated team member. Notify MHRA via email once the final result is posted.

5.7 Other Regulatory Approvals

There are other regulatory approvals which may be required depending on the type of project such as CAG (Confidentiality Advisory Group), ARSAC etc. and hence the project filters on IRAS application should be completed carefully. It is also Sponsor's responsibility to see that all the approvals required for the project are being sought.

6. Related Documents

GOSH R&D SOP Study Documentation and Monitoring, Audit and Inspection GOSH/ICH/SOP/R/006
Pharmacovigilance and Safety Reporting SOP GOSH/ICH/SOP/R/007
MHRA submission portal guidelines
Amendments SOP GOSH/ICH/SOP/R/005
Amendment Log

7. References

MHRA website
HRA Website
EudraCT website
IRAS guidance

8. Appendices (If applicable)

All related documents available on GOSH Web.