Glo-BNHL Industry Information Pack

Guidance: post-asset inclusion v2.0

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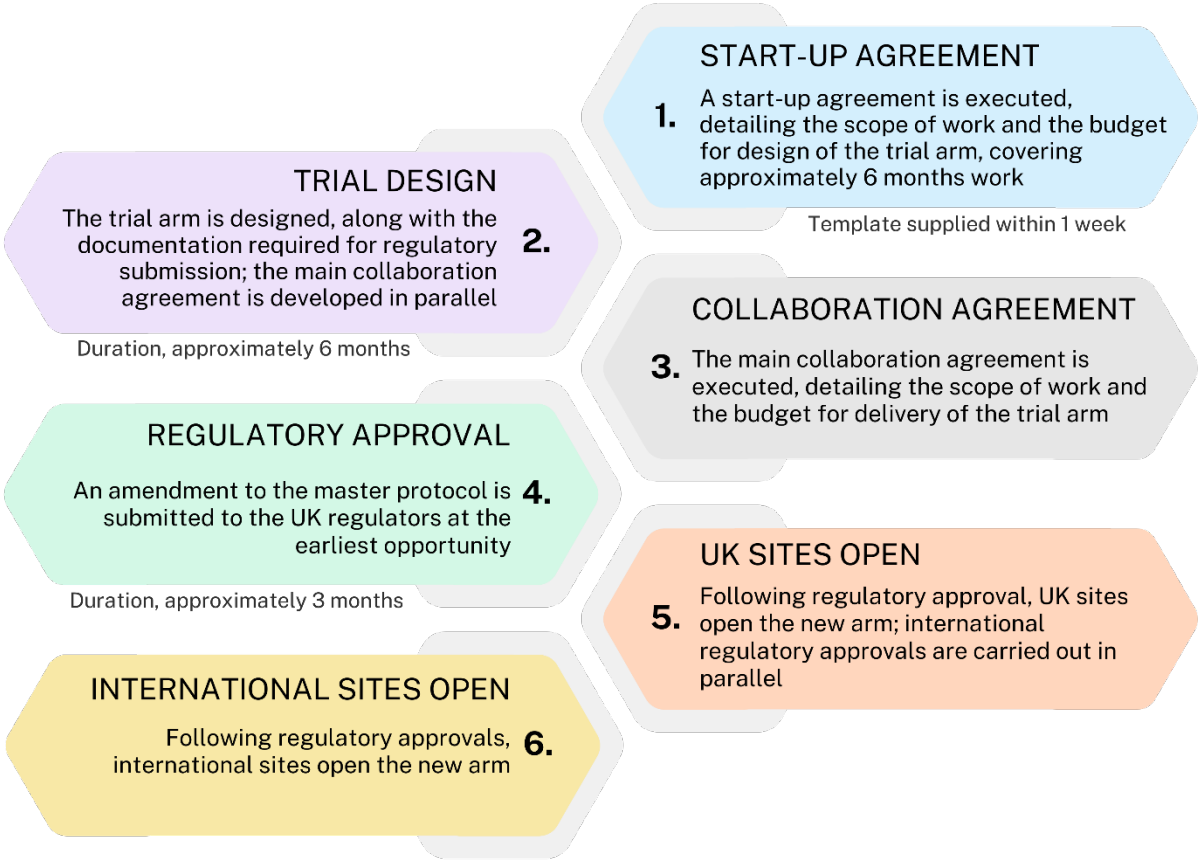
Overview

The Glo-BNHL platform trial is Sponsored by the University of Birmingham and is managed by the Cancer Research UK Clinical Trials Unit (CRCTU) at the University of Birmingham, in accordance with its procedures. Glo-BNHL is an international, academic-led clinical trial which will be conducted according to International Conference on Harmonisation Good Clinical Practice (ICH GCP) standards to facilitate regulatory submissions. The aim is to produce data to support marketing authorisation applications.

Agreements with industry collaborators will be organised between the University of Birmingham, as Sponsor, and the industry collaborator. Agreements will be acknowledged by the Chief Investigator, Professor Amos Burke. The key principles of university-sponsored trials with industry collaborators can be found in Appendix I. The University of Birmingham will also enter into separate agreements with associated third-parties, as required.

The CRCTU holds an extensive Quality Management System covering all aspects of clinical trial management, from design through to study closure and archiving; a summary of topics is included in Appendix II. A full list of Standard Operating Procedures is available upon request.



Start-up Agreement

Following formal notification of prioritisation for inclusion in Glo-BNHL, a start-up agreement will be executed between the University of Birmingham and the asset-holder, agreeing the scope of work and budget for the design of the trial arm. This design work is funded by the asset-holder in its entirety.

An existing template of the start-up agreement is available on request, detailing work covering a period of approximately 6 months, during which time the trial management team will work with the asset-holder to refine the design of the trial arm and develop the documents required for regulatory submission. Regular collaborative meetings will be held between the trial management team and the asset-holder; documents will be reviewed by the asset-holder and comments taken into account by the trial management team. The expectation is that the main collaboration agreement is developed in parallel.

A commitment to execute both agreements in an expedited fashion is imperative to the smooth running of the trial.

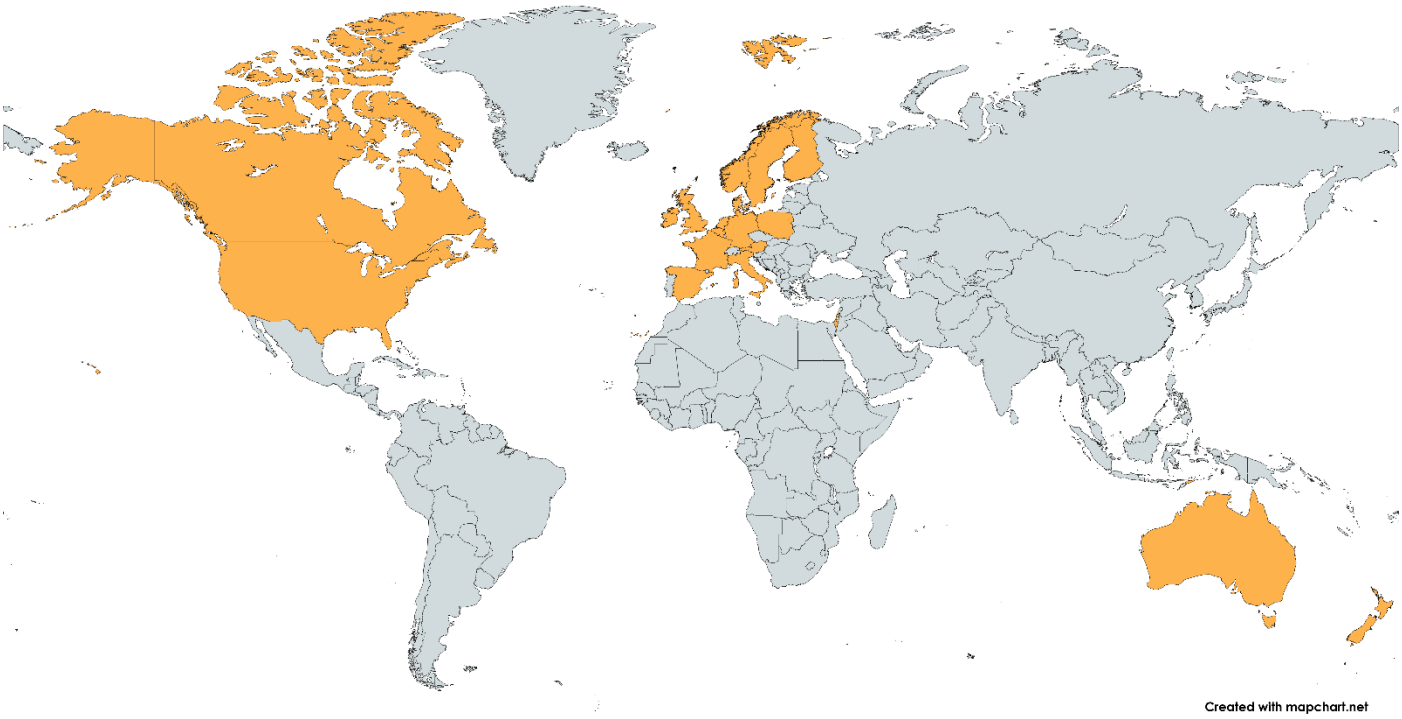
Main Collaboration Agreement

Upon completion of the scope of work detailed in the start-up agreement, no further work will be completed until the main collaboration agreement is executed. At this point the asset-holder will not be obligated to continue beyond the start-up agreement. Provided both parties are in agreement to continue, the main collaboration agreement will be executed, detailing the scope of work and the budget for delivery of the trial arm from regulatory submission to closure and analysis. The asset-holder funds delivery of the individual arm of the study in its entirety.

Upon execution of the main collaboration agreement, an amendment to the existing platform trial will be submitted to the UK regulators at the earliest opportunity. UK regulatory approval is expected to take around 3 months and, once approved, existing UK sites will open the new arm of the study. International regulatory submissions in exisiting territories will take place in parallel with UK site activation. International sites will open as and when approvals are granted in each territory.

Country and Site Management

The CRCTU has a well-established, international network of paediatric centres, with the expertise to deliver complex oncology trials. The University of Birmingham delegates certain country-specific Glo-BNHL activities to National Coordinating Centres (NCCs) in each country. This is usually a lead academic institution to which the University of Birmingham delegates some of the Sponsor responsibilities. NCCs are typically responsible for obtaining and maintaining regulatory approvals, for identifying and managing participating sites and for managing the trial conduct within their territories. As Sponsor, the University of Birmingham retains oversight of the conduct of the NCCs. The University of Birmingham contracts directly with UK sites and with NCCs; NCCs contract with participating centres within their territories.



Planned territories: Australia/New Zealand, Austria, Belgium, Canada, France, Germany, The Republic of Ireland, Israel, Italy, The Netherlands, The Nordic Region, Poland, Spain, The United Kingdom and The United States of America.

Additional Requirements

In order to set up and manage the study efficiently, the CRCTU will require the following information, including any future updates where applicable:

- Investigators' Brochure
- Investigational Medicinal Product (IMP) Dossier or cross-referral letter
- Details of supply, labelling and manufacture of IMP
- Accepted safety information/language relating to IMP
- Details of approved Paediatric Study Plan and Paediatric Investigation Plan or drafts and timelines for submission

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Appendix I - Key principles of university-sponsored trials with industry collaborators

The University of Birmingham recognises the importance of executing contracts in a timely manner. To support the process, this document outlines some key principles we adhere to when drafting and agreeing contracts for University-sponsored clinical trials with industry collaborators. Please note that these may not apply to other types of research.

Trial design and protocol

The CRCTU designs collaborative clinical trials and develops the trial protocols with welcome and expected input from the asset-holder. As Sponsor, the university is responsible for final approval of the protocol and subsequent amendments as required by the regulators.

Regulatory inspections

The CRCTU will notify the asset-holder if a regulatory inspection relates to the collaboration. The University of Birmingham cannot however accept a contractual clause that requires notification of any inspection across the university as a whole. The size of the university's research portfolio makes this impracticable.

Auditing

The CRCTU welcomes audit of the trials unit by the asset-holder. Independent audit of individual trial sites is not possible. As the trial Sponsor, this remains the responsibility of the University of Birmingham. Co-audits are acceptable, the details of which can be included in the main collaboration agreement.

Liability

The University of Birmingham is a charitable organisation and therefore limits the liability of assets. For this reason, liability will only be accepted for direct losses caused by a trial. A reasonable ceiling for any liability costs will be detailed in the main collaboration agreement.

Regulatory standards

The CRCTU works to Good Clinical Practice (GCP) standards as defined in the EU Clinical Trials Regulation (Regulation 536/2014) and as required by the Medicines for Human Use (Clinical Trials) Regulations, 2004 (and subsequent amendments). Industry-collaborative trials with intention to use the data for filing purposes will adhere to ICH-GCP guidelines.

IMP supply and distribution

A copy of the current approved Investigator's Brochure is required before work can commence. Where an Investigational Medicine Product Dossier (IMPD) is available, the asset-holder must supply this to the CRCTU or provide a cross-referral letter for the purpose of regulatory submissions. The assistance of the asset-holder is also required when preparing the application for initial Clinical Trial Authorisation.

The CRCTU requires information about how the IMP under evaluation will be sourced, labelled and distributed. Responsibilities are agreed upon in the main collaboration agreement. The asset-holder is required to warrant that supply of IMP is in accordance with Good Manufacturing Practice and that it is supplied in a form that is appropriately labelled for use as an IMP in all participating countries with appropriate qualified person release where required. In order to facilitate timely availability of IMP, it is advisable for the asset-holder to have early discussions with the CRCTU.

Drug distribution services to participating centres should be provided by the asset-holder. In the event that these services are required to be organised by the CRCTU, the University of Birmingham's procurement procedures must be followed, which may include going to tender; this has resource implications and may impact the trial delivery timeline.

Appendix I continued - Key principles of university-sponsored trials with industry collaborators

Safety reporting

As Sponsor, the University of Birmingham is responsible for Glo-BNHL pharmacovigilance, and therefore University of Birmingham and CRCTU processes and procedures will be followed. Serious Adverse Events (SAEs) will be collected via the electronic data capture (EDC).

SAEs will be reported to the asset-holder according to a pre-agreed format within an agreed timeframe, beginning when the CRCTU becomes aware of the incident. A reporting timeframe from occurrence of the incident cannot be agreed to. The CRCTU will endeavour to obtain additional data about a SAE where this is reasonable and specifically requested.

Additional safety data can be provided, if reasonable for the type of trial, but must be defined in advance of contractual negotiations due to cost implications.

The asset-holder is expected to provide the University of Birmingham with relevant safety data about the IMP on an on-going basis throughout the trial. This is to assist the university in meeting its regulatory safety reporting obligations. Quarterly line listings of suspected unexpected serious adverse reactions (SUSARs) is requested.

Termination

Due causes for termination can be detailed in the main collaboration agreement; termination without due cause will not be an option.

In the event of termination, the asset-holder is expected to work with the CRCTU to safely close the study. It should be noted that often there are costs relating to a study that are non-cancellable. Closing out a trial in a manner that is ethical and safe for patients is also likely to incur additional costs. The asset-holder will need to agree reasonable provision to cover early termination.

Publication

The University of Birmingham welcomes and anticipates review of and comments on any proposed publications resulting from the relevant treatment arm and will work with the asset-holder to ensure non-disclosure of any commercially sensitive or confidential information. The university retains the right to publish the findings of the study, irrespective of outcome. The Glo-BNHL Publication Plan details planned publications; maintenance of this plan is the responsibility of the Sponsor. A redacted version will be shared with collaborators upon request.

Intellectual Property (IP)

Any existing IP belonging to either party will remain with that party.

Any new IP that results from the study and is solely related to the asset-holder's IMP is owned by the asset-holder.

Typically, any IP resulting from the study that is not solely related to a single asset-holder's IMP will be owned by the University of Birmingham as Sponsor. The university will be free to use it for any non-commercial academic purpose. The proposed budget will include a fair and reasonable recompense to account for possible commercial exploitation by the asset-holder.

Appendix I continued - Key principles of university-sponsored trials with industry collaborators

Data sharing and regulatory standards for data

The terms and level of data sharing will be outlined in the main collaboration agreement. Routinely, the CRCTU provides a comprehensive end-of-trial summary report. For industry-collaborative trials, ICH-GCP compliant, patient-level raw data and aggregated data will be shared after recruitment to the treatment arm has completed to enable the asset-holder to pursue marketing authorisation. Asset holders will not have access to the database.

Interim transfers of patient-level raw data will not take place while the treatment arm is recruiting unless analysis is required to be performed by the asset-holder which is critical to the operation of the trial, for example to enable pharmacokinetic analysis to be conducted during the trial which may help to inform trial decision making. Where interim data transfers are required, these will be defined and agreed upon in advance and will not contain efficacy data.

Additional documentation required for regulatory submission will also be provided by the University of Birmingham and will be referenced in the main collaboration agreement.

Payment timelines

Clinical trials have significant upfront and early-stage costs, therefore payment timelines must reflect this. Often there is a need to recruit dedicated staff for a new treatment arm; this must therefore be considered when defining payment and set-up timelines.

Appendix II - CRCTU Quality Management System topics

Advanced Therapy Medicinal Products
Archiving
Audits
Blinded Trials
Case Report Forms
Clinical Trial Management
Committees
Data Management Procedures
Database Lock
Data Sharing
Deviations
Dose Finding Trials
End of recruitment, trial and site closure
Ethics and Regulatory
Finance Management
Human Tissue and Laboratories
Informed Consent Procedures
International Trials
Information Technology Systems
Medical Devices
On-site Monitoring
Pharmacovigilance
Product Information
Project Set-up
Project Set-up when CRCTU acts as a site
Protocol development and amendment
Quality Management Procedures
Randomisation
Shared Care Centres
Site Initiation
Statistical Procedures
Training
Trial Master File
Trial Medication
Trial Quality Management
Trial Systems