Reference Number: UHB543 Version Number: 2	Date of Next Review: 15/04/2029

Cardiff Joint Research Office (JRO) Applying for Sponsorship of Higher Risk Studies (including Clinical Trials of Investigational Medicinal Products (CTIMPs) and Clinical Trials of Medical Devices (Medical Device Trials))

Standard Operating Procedure (SOP)

This SOP will be implemented from the 28th of Apr 2026 to align with The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 coming into force

Introduction and Aim

In accordance with the UK Policy Framework for Health and Social Care Research (UKPF), the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended (referred to throughout this document as The Regulations) and the UK Medical Device Regulations 2002 (UK MDR 2002), as amended, all health and social care research studies must have an identified Sponsor. In accordance with The Regulations, the Sponsor is defined as: "…the person who takes responsibility for the initiation, management and financing (or arranging the financing) of that trial". The Sponsor must confirm that there are adequate arrangements to initiate, manage, monitor and finance a Clinical Trial of an Investigational Medicinal Product (CTIMP) or Clinical Investigation of a Medical Device (Medical Device Trial).

Prior to accepting the role of Sponsor of a study deemed to present a higher risk, including a CTIMP or Medical Device Trial, Cardiff and Vale University Health Board (CAVUHB) or Cardiff University (CU) must undertake a risk assessment process to ensure that Sponsorship conditions are met.

This SOP describes the process for applying for Sponsorship for studies deemed to present a higher level of risk, including CTIMPs or Medical Device Trials from CAVUHB or CU, via the Cardiff Joint Research Office (JRO). The Sponsorship application and review process is overseen by the JRO Research Governance Team.

Objectives

To explain the JRO research governance Sponsorship application process for trials which are categorised as high risk in accordance with the JRO Sponsor Risk Assessment process, including CTIMPs or Medical Device Trials and which are:

- led by CAVUHB or CU (i.e. where CAVUHB or CU employee(s) have led on the design of the trial, where either organisation is the lead grant recipient, or where significant elements of the trial are to be delivered and managed by CAVUHB or CU).
  AND
- where CAVUHB or CU have been approached to take on the role of Sponsor.

Scope

This SOP applies to the process for applying for CAVUHB and CU Sponsorship for the following categories of **higher risk** research studies:

i. Clinical Trials of Investigational Medicinal Products (CTIMPs) falling under the scope of the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended). That is, any research investigation with human participants, other than a non-interventional trial, which is intended:
   a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products,
   b) to identify any adverse reactions to one or more such products, or
   c) to study absorption, distribution, metabolism and excretion of one or more such products,

with the object of ascertaining the **safety or efficacy** of those products.

ii. Clinical investigations of medical devices falling under the scope of the UK MDR. That is, any investigation of one or more of the following:
   a) An in-vitro diagnostic medical device;
   b) an active implantable medical device;
   c) A device for performance measurement;
   d) Medical device standalone software, including apps.

AND where the applicant is intending to apply for UK Conformity Assessment (UKCA) marking, Conformité Européene (CE) marking or CE UK and Northern Ireland (CE UKNI) marking.

iii. Combined clinical trials of both an Investigational Medicinal Product (IMP) and a medical device.
iv. Advanced Therapy Investigational Medicinal Products (ATIMPs)
v. Other clinical trial to study a novel intervention or randomised clinical trial or randomised clinical trial to compare interventions in clinical practice (including surgery trials)
vi. Platform Trials
vii. International Trials
viii. Other types of health and social care research (also known as clinical research) falling under the scope of the UK Policy Framework for Health and Social Care (UKPF) UKPF and categorised as high risk by the JRO (in accordance with its Costing Model).

This SOP does **not** apply to the following categories of activity:

- work which is wholly categorised as Public and Patient Involvement (PPI).
- projects meeting the criteria for service evaluation, audit or quality improvement which should be referred to the appropriate CAVUHB department.

- commercially Sponsored research.
- clinical research studies classified by the JRO as low or medium risk. The process for applying for Sponsorship for these types of studies is covered in the SOP for *Applying for JRO Sponsorship- Low and Medium Risk Studies* (SOP-001-04).
- student-led projects or studies being carried out for the purposes of an educational qualification. The process for applying for Sponsorship for these types of studies is covered in the SOP for *Applying for JRO Sponsorship- Low and Medium Risk Studies* (SOP-001-04).

Projects meeting the criteria for service evaluation, audit or quality improvement and which are led by CAVUHB employees, should liaise with the CAVUHB Quality Improvement department.

Where the categorisation of a project is not clear, staff may consult the HRA's 'Defining Research' table, use the HRA's 'Is my study research?' decision tool, or request an Early Project Review meeting via the JRO (refer to section 3.2 of this SOP).

Where the regulatory status of a trial is not clear (i.e. it is not clear whether it meets the definition of a CTIMP or Medical Device Trial), research staff should first consult the MHRA's 'Is it a Clinical Trial of a Medicinal Product?' algorithm tool or speak with the MHRA's Device Helpline Team (Devices.Borderlines@mhra.gov.uk) for queries about borderline medical devices. The JRO reserves the right to seek further opinion on the proposed regulatory status of a trial and may do so by seeking further advice or clarification from those deemed to be experts in the field.

Responsible Personnel:

All Chief Investigators (CIs), Principal Investigators (PIs) and Research Team members from both CAVUHB and CU, who are working on or planning to conduct a CAVUHB or CU Sponsored CTIMP, Medical Device Trial or studies meeting the JRO criteria for high risk are required to read and familiarise themselves with this SOP. Guidance on who can act as a CI of a higher risk study (including specific rules around who can assume the role of CI in a CTIMP or Medical Device Trial) is included in section 4.0 of this SOP.

The JRO Research Governance Team is responsible for authoring, reviewing and updating this SOP. The JRO Quality Management Group is responsible for reviewing the SOP. The joint Clinical Trials Governance Group (CT-GG) and Joint Research Governance Group (JRGG) are responsible for approving the SOP.

Equality Health Impact Assessment	An Equality Health Impact Assessment has been completed on the Research Governance Policy and Procedure (UHB099) under which this procedure sits.

Documents to read alongside this Procedure	UK Policy Framework for Health and Social Care Research 2017 - https://www.hra.nhs.uk/planning-and-improving-researchliciesstandards-legislation/uk-policy-framework-health-social-careresearch/
Approved by	Clinical Trials Governance Group (CT-GG) Joint Research Governance Group (JRGG)
Accountable Executive or Clinical Board Director	Medical Director
Author(s)	JRO Research Governance Team

Disclaimer

If the review date of this document has passed please ensure that the version you are using is the most up to date either by contacting the document author or the Governance Directorate.

Summary of reviews/amendments

Version Number	Date of Review Approved	Date Published	Summary of Amendments
1.0	30/01/2025	XXXX	This is a new SOP, that replaces UHB453. Major updates implemented to reflect the formation of the JRO and the alignment of the Sponsorship application and risk assessment processes for both CAVUHB and Cardiff University.
2.0	15/04/2026	24/04/2026	• Updated scope, expanded to include (1) Advanced Therapy Investigational Medicinal Products (ATIMPs) (2) Other clinical trial to study a novel intervention or randomised clinical trial or randomised clinical trial to compare interventions in clinical practice (including surgery trials) (3) Platform Trials (4) International Trials

			• Update on who can be a CI to align with The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 • Introduction of new terminology due to updated CT regulations. 'Amendments' replaced with 'modifications', • Change of terminology for JRO process, EPR replaced with PIM

Contents

1.0 DEFINITIONS/ABBREVIATIONS

ARSAC	Administration of Radioactive Substances Advisory Committee
ATIMP	Advanced Therapy Investigational Medicinal Products
C&C	Capacity and Capability
CAG	Confidentiality Advisory Group
CAVUHB	Cardiff and Vale University Health Board
CE	Conformité Européene (CE)
CI	Chief Investigator
CRO	Contract Research Organisation
CTIMP	Clinical Trials of Investigational Medicinal Products
CTU	Clinical Trials Unit
CU	Cardiff University
DMP	Data Management Plan
DSUR	Development Safety Update Report
HCRW	Health and Care Research Wales
HRA	Health Research Authority
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
JRO	(Cardiff) Joint Research Office
MHRA	Medicines and Healthcare Products Regulatory Agency
mNCA	Model Non-commercial Clinical Trial Site Agreement
OID	Organisation Information Document
PI	Principal Investigator
PIF	Project Initiation Form
PIM	Project Initiation Meeting
PPIE	Patient and Public Involvement and Engagement
QMG	Quality Management Group
RAF	Risk Assessment Framework
REC	Research Ethics Committee
R&D	Research and Development
SAP	Sponsor Assessment Process
SIV	Site Initiation Visit
SOP	Standard Operational Procedure

SoE	Schedule of Events
SoECAT	Schedule of Events Cost Attribution Template
Sponsor	The individual, company, institution or organisation, which takes on the ultimate responsibility for the initiation, (management or arranging the initiation) of and/or financing (or arranging the financing) for that research
TMF	Trial Master File
UKCA	UK Conformity Assessment
UK-CRC	UK Clinical Research Collaboration
UKPF	UK Policy Framework for Health and Social Care Research 2017 (as amended)

2.0 GENERAL INFORMATION

All health and social care research requires a Sponsor. In the context of research governance, the Sponsor is an organisation, individual or partnership that takes responsibility for the quality and conduct of a research study. In accordance with the Regulations and the UKPF (as amended), the Sponsor is responsible for the initiation, management and financing (or arranging the financing) of a health and/or social care research study and has specific responsibility for the following areas:

i. identifying and addressing poorly designed or planned research and poor-quality research proposals, protocols or applications and ensuring that research proposals and protocols.
ii. satisfying itself that the investigators, research team and research sites are suitable.
iii. ensuring that roles and responsibilities of the parties involved in the research and any delegation by the sponsor of its tasks are agreed and documented.
iv. ensuring adequate provision is made for insurance or indemnity to cover liabilities which may arise in relation to the design, management and conduct of the research project.
v. ensuring appropriate arrangements are made for making information about the research publicly available before it starts (where appropriate).
vi. agreeing appropriate arrangements for making data and tissue accessible, with adequate consent and privacy safeguards, in a timely manner after it has finished.
vii. ensuring arrangements for information about the findings of the research are made available.
viii. ensuring that, where expected or required, the research has approval from a research ethics committee and any other relevant approval bodies before it begins.
ix. verifying that regulatory and practical arrangements are in place, before permitting the research to begin in a safe and timely manner.

x. putting and keeping in place arrangements for adequate finance and management of the research project, including its competent risk management and data management.

xi. ensuring that effective procedures and arrangements are kept in place and adhered to for reporting (e.g. progress reports, Pharmacovigilance and safety reports) and for monitoring the research, including its conduct and the ongoing suitability of the approved proposal or protocol in light of adverse events or other developments.

xii. the manufacture and labelling of Investigational Medicinal Products (IMPs), where applicable

Sponsor responsibilities may be delegated as appropriate. For high-risk studies, this will be documented in a trial-specific Memorandum of Understanding (MoU) and/or appropriate contractual arrangements (see section 5.2).

All health and social care research requiring CAVUHB or CU Sponsorship must be discussed with the Cardiff JRO at the study development or grant application stage. The CI (or their delegate) should arrange a Project Initiation Meeting (PIM) with the JRO during the study design or grant application phase. All trials meeting the JRO's criteria for higher risk studies must be appropriately costed. All CTIMPs and Medical Device Trials must have adequate levels of funding in place to support the running of the trial from set-up to archiving. CAVUHB and CU will not consider Sponsorship of unfunded CTIMPs or Medical Device Trials.

The JRO Research Governance Team will provide guidance regarding the requirements of the Sponsor Assessment Process (SAP) (see section 5.0 of this SOP) in order to facilitate the application. The SAP must be completed and Sponsorship in Principle confirmed, prior to the CI submitting the study to the relevant approval bodies and regulatory authorities (e.g. the MHRA, HRA/HCRW and NHS RECs and other bodies as appropriate, such as the Confidentiality Advisory Group (CAG)).

3.0 PROCEDURES

3.1 WHEN TO REQUEST SPONSORSHIP OF HIGHER RISK STUDIES

The appropriate Sponsoring organisation is normally determined by the employment status of the proposed Chief Investigator (CI) and/or the organisation leading on the grant application. Sponsorship will normally be considered for studies led by CIs whose primary contract of employment is with CAVUHB or CU (see Section 4.0 of this SOP).

It is recommended that the CI or study lead contacts the JRO Research Governance Team for initial advice as early as possible during the study development and grant application phase. The contact details for the relevant CAVUHB/CU team are:

Proposed Sponsor organisation	**Contact email address**
Cardiff and Vale UHB	research.governance@wales.nhs.uk
Cardiff University	resgov@cardiff.ac.uk

3.1.1 Procedure for studies applying for funding

The CI (or their delegate) should liaise with the JRO Research Governance Team as early as possible to discuss the Sponsor Assessment Procedure (SAP) and to arrange a JRO PIM.

For higher risk studies, CAVUHB or CU employees should arrange a PIM prior to submitting the grant application (see point 3.2 of this SOP).

Where a study meets the JRO criteria for moderate or higher-level additional contracts and research governance support, the CI may be asked to cost in additional staff costs to cover contracts and research governance resource. This will be discussed during the PIM. Requirements for additional JRO support is determined based on the JRO Costing Model (available upon request).
A further follow-up meeting should then be arranged if the funding application is successful or reaches the second round.

The following Pre-Awards teams should be contacted for assistance with costing a grant application for a higher risk study:

Employing organisation of the CI	**Pre-Awards Team Contact**	**Email address**
CAVUHB	CAVUHB Grants Team	Research.GrantSupport@wales.nhs.uk
CU	School of Medicine Research Office (for staff in MEDIC, HCARE and DENTL). Researchers from other CU academic schools should contact their Research Office or Central CU Pre-Awards	Somres@cardiff.ac.uk

A Schedule of Events Costs Attribution Template (SoECAT) form is usually required to be completed as part of the grant application (for UK funding bodies). Guidance on the completion of the SoECAT Form is available from the NIHR. Assistance with obtaining CAVUHB NHS costings may be sought from the CAVUHB Pre-Awards contact (above).

3.1.2 Procedure for unfunded studies

All studies meeting the JRO's definition of high risk will be required to secure adequate funding for the duration of the trial, from study set-up through to archiving. CAVUHB and CU are unable to Sponsor unfunded CTIMPs and Medical Device Trials.

3.2 Arranging a JRO Project Initiation Meeting (PIM)

The PIM meeting is the first stage in the Sponsorship application process. Studies led by either CAVUHB or CU are required to arrange an PIM meeting with the JRO. CIs (or their delegates) should request a PIM, submitting a Project Initiation Form (PIF) through the JRO website
(New Study - Cardiff Joint Research Office (cardiffjro.com)).

The purpose of the PIM is to confirm the following:

i. the categorisation of a project in accordance with the NHS definition of research (i.e. that it intends to generate generalisable new knowledge). Studies meeting the criteria for service evaluation, quality improvement or clinical audit do not fall within the remit of the JRO and will be directed towards the relevant CAVUHB/CU department.
ii. for funded studies- whether any additional contracts or research governance support is required to manage the study and whether this can be incorporated into the grant application stage (determined in accordance with the JRO Costing Model- refer to Table 1 of this SOP).
iii. which organisation will be the most appropriate Sponsor for the study.
iv. the management arrangements for higher risk studies and to ensure that appropriate staff resource is available to run the trial, via the appointment of a Clinical Trials Unit (CTU) and/or Contract Research Organisation (CRO).
v. the ethical and governance approvals that will likely be required for the project following an initial discussion, as well as discussing any potential barriers to gaining these approvals.
vi. the relevant JRO Research Governance Team contact to take the application forward.

3.3 Eligibility for Sponsorship

To be eligible for Sponsorship from either CU or CAVUHB, the following requirements must be fulfilled for higher risk studies:

i. the CI must hold a substantive contract of employment with either CU or CAVUHB; AND
ii. CU or CAVUHB will be the primary grant holder; AND
iii. a UK-Clinical Research Collaboration (UK-CRC) accredited Clinical Trials Unit (CTU) must be appointed (in the case of CTIMPs and Medical Device Trials and occasionally other trials meeting the definition of high risk). In some cases, where specialist support is required from a non UK-CRC accredited unit or department (in the case of Medical Device Trials for example), it may be possible to adopt a hybrid approach to CTU oversight and input. This will be discussed at the PIM stage.

Other Sponsorship eligibility factors may also apply and will need to be discussed with the JRO, these include (but are not limited to):

- if the study is appropriately designed and is deliverable.
- if there are plans to involve international sites.

Eligibility for Sponsorship is confirmed during the PIM meeting. **Please note that this does not constitute confirmation of Sponsorship in Principle. Confirmation of Sponsorship in Principle of a higher risk study is subject to the conditions outlined in Section 5.0 of this SOP being met.**

3.4 JRO Project Set-Up Meeting

For CTIMPs, Medical Device Trials and studies deemed to be higher risk, the JRO Director may determine that additional Project Set-Up Meetings are required following the initial PIM m and before Sponsorship in Principle approval is granted. Additional Project Set-Up Meetings may be arranged following confirmation of funding, or where further information and detail about the study is required. Project Set-Up Meetings are agreed following the initial PIM and are arranged via the JRO Administrative team.

4.0 WHO CAN ACT AS CI OF A HIGHER RISK TRIAL?

4.1 Who can act as a CI of higher risk studies (excluding CTIMPs, Medical Device Trials or Combined Trial of an IMP and Medical Device)?

A CI must be appointed for all studies to be Sponsored by CAVUHB or CU. Throughout this SOP, the term ‘CI’ is used to refer to the individual leading the specific study (normally the individual who is responsible for designing the study protocol and/or the named lead grant recipient, in the case of funded studies). The CI may delegate their duties as appropriate to other suitably

qualified members of the study team (e.g. Clinical Research Fellows, nursing and Allied Health Professional staff, NHS Principal Investigators, Pharmacists, Research Associates, Trial Managers, Statisticians, Technicians and Data Managers). However, the CI is considered by the JRO to hold overall responsibility for the design, conduct and management for the study and will ordinarily hold a contract of employment with either CU or CAVUHB.

In circumstances where the CI is not employed by CU or CAVUHB, the JRO may consider Sponsorship provided that:

i. the funding is being awarded to either CU or CAVUHB.
ii. the study will be managed by CU or CAVUHB (e.g. by a CU or CAVUHB CTU or department).
iii. an appropriate agreement is established with the external CI, which adequately details their roles and responsibilities in relation to the conduct of the study.

It is not suitable for students and Postgraduate Researchers (PGRs) to take on substantive roles in higher risk studies, CTIMPs and Medical Device Trials and the CI should not delegate trial responsibilities to students. It is accepted that PGRs may occasionally work on analysing completed datasets or sample collections derived from such studies and trials, for the purposes of an educational qualification. Students should not lead on work which contributes to key trial endpoints in these categories of trials.

4.2 Who can act as a CI of a CTIMP, Medical Device Trial or a Combined Trial of an IMP and Medical Device?

For CTIMPs, the CI must be an authorised health professional (as defined by the Regulations), that is: -

- a doctor
- a dentist
- a registered nurse as defined in regulation 8(1) of the Human Medicines Regulations 2012
- a pharmacist
- a person registered in a register of ophthalmic opticians maintained under section 7(a) of the Opticians Act 1989
- a person registered in the Health and Care Professions Council register (as defined in regulation 8(1) of the Human Medicines Regulations 2012) as a member of a relevant profession within the meaning of article 2 of, and paragraph 1 of Schedule 3 to, the Health Professions Order 2001
- a registered osteopath as defined by section 41 of the Osteopaths Act 1993

- a registered chiropractor as defined by section 43 of the Chiropractors Act 1994
- a person registered under the Anaesthesia Associates and Physician Associates Order 2024
- a registered midwife as defined in regulation 8(1) of the Human Medicines Regulations 2012

For device studies under current UK medical device regulations, the CI must:

- Be appropriately qualified and have sufficient expertise relative to the device and its intended use.
- Be capable of taking overall responsibility for the study
- Usually be based in the UK
- Be named on IRAS and accountable for regulatory compliance

- Come from any relevant professional background (clinical, academic, scientific), provided they meet competency expectations

It may be is possible to appoint a CI who does not meet the criteria listed above, to lead on CTIMPs and Medical Device Trials, provided that a suitably experienced and qualified clinical co-CI is also appointed to the trial.

Any individual appointed to act as a CI or co-CI is required to sign a Memorandum of Understanding (MoU) (or appropriate contractual arrangement) detailing their roles and responsibilities in the study (see section 5.2).

5.0 SPONSOR ASSESSMENT PROCEDURE (SAP) FOR HIGHER RISK STUDIES

During the PIM , a Lead Sponsor Reviewer will be assigned to the study. The Lead Sponsor Reviewer will be a member of the JRO Research Governance Team, and this individual will oversee the Sponsor Assessment Procedure (SAP). The SAP is intended to assess:

- that the study has been designed and will be conducted in line with the relevant Regulations and Good Clinical Practice (GCP); *
- the arrangements for the proposed study intervention(s) and IMPs (in the case of CTIMPs), such as pharmacy support and manufacturing arrangements; *
- whether the study is adequately costed; *
- the feasibility of the study design.
- the study management and monitoring arrangements; *
- the scientific integrity and quality of the study design; *
- the financial and contractual arrangements for the study. *

- Excess Treatment Costs (ETC) application process (if applicable) and NHS costings.
- scoping of potential vendors/service providers (in accordance with the JRO SOP for Vendor Assessment- SOP/001/06).

At any point during the SAP, the Lead Sponsor Reviewer may request further information from the CI (or their delegate) and may request updates to the documents included in the Sponsorship Application (see section 5.2 of this SOP) in order to ensure compliance with the relevant procedure, policy or area of legislation. The Lead Sponsor Reviewer may also seek further advice and input from departments external to the JRO, such as:

- CAVUHB Information Governance/ CU Data Protection Team;
- Human Tissue Act experts.
- CAVUHB/CU Contracts Teams.
- CAVUHB/CU Pre-Awards Teams and/or Finance Department.
- NHS Radiology and/or Medical Physics Departments.
- NHS Pharmacy teams.
- NHS Support departments.
- NHS directorate managers/R&D leads.
- CU academic school management.

The JRO operates a three stage Sponsor Assessment Procedure (SAP) for CTIMPs and Medical Device Trials and a two stage SAP for higher risk studies. The stages of the SAP are outlined below.

5.1 Stage 1: Pre-funding

Expected outcome of Stage 1 of the SAP: by the end of Stage 1, the JRO will have confirmed whether it can support the funding application, and a Sponsor Organisation will have been agreed. The study will have been assigned a Lead Sponsor Contact.

i. a PIM should be arranged with the JRO prior to the submission of the funding application (outlined in section 3.0 of this SOP). Following the PIM, the CI (or their delegate) should liaise with the relevant Lead Sponsor Contact (as agreed at the PIM) to arrange initial Sponsor in Principle support for the funding application. Sponsor in Principle support for the funding application does not constitute final Sponsor approval to submit to a Research Ethics Committee (REC) and/or Competent Authority.
ii. where required by the funder, a letter confirming provisional Sponsorship support (pre-funding) can be provided by the Lead Sponsor Contact.
iii. electronic Sponsor sign-off of the funding application may be required at this stage. Pre-funding Sponsorship in Principle does not constitute final Sponsor approval to commence the study and all higher risk studies are required to complete all relevant stages of the SAP.

If the funding is successful, the CI should contact the Lead Sponsor Contact to commence Stage 2 of the SAP. The funding Terms and Conditions will need to be agreed and signed by the authorised signatory in either CU or CAVUHB, prior to the commencement of Stage 2.

If the funding is unsuccessful, the SAP will either be paused or closed. The CI will be required to book a further PIM if further funding applications are pursued for the trial.

5.2 Stage 2: Sponsorship in Principle- Permission to apply for regulatory and REC approvals (and other approvals as required)

Expected outcome of Stage 2 of the SAP: by the end of Stage 2, the Lead Sponsor Contact should be in a position to issue Sponsorship in Principle approvals, and the CI will normally be in a position to submit the IRAS application.

Upon confirmation of a successful funding application, the CI (or their delegate, e.g. a Trial Manager) should inform their appointed Lead Sponsor Contact. Project Set-Up meetings may then be arranged between the trial team and the Lead Sponsor Contact (in addition to other members of the JRO as required).

The following activities will normally take place during Stage 2 of the SAP for higher risk studies:

i. development of the study Protocol, Participant Information Sheets and Informed Consent Form and other Essential Documents required for the REC and/or request to the Competent Authority. Together, these documents form the Sponsorship Application. The development of study documents is led by the CI and research team and should involve adequate Patient and Public Involvement and Engagement (PPIE), with the Lead Sponsor Contact providing input as required. In the case of CTIMPs and Medical Device Trials, the development of the Protocol and study documents required for the REC and MHRA submission should follow the templates provided by the appointed CTU and incorporate appropriate critical to quality factors as defined by the CTU Other types of higher risk studies should follow the JRO Protocol template. Participant-facing documents should be designed in accordance with the HRA Quality Standards and Design Standards. The final draft versions of all essential documents necessary for the submission to the REC and/or MHRA are subject to the Sponsor's approval.

A full list of the essential documents required for a Clinical Trial Application (CTA) is available on the Combined IRAS portal. Guidance is also available on the MHRA website.

ii. completion of a study risk assessment. For higher risk projects managed by a CTU, the CTU risk assessment process should normally be followed (subject to agreement with the JRO). Higher risk projects which do not involve a CTU will be subject to the JRO Sponsor risk assessment process as detailed in *Applying for JRO Sponsorship- Low and Medium Risk Studies* (SOP-001-04). The study risk assessment is used to assess and document the risk level of the study and determines the Sponsor oversight and monitoring arrangements for the study. It should be reviewed regularly throughout the life of a study, and following all substantial modifications.

iii. finalisation of the NHS site costings and the trial Schedule of Events Cost Attribution Tool (SoECAT).

iv. contractual arrangements necessary to permit the submission to the REC and Competent Authority. This may include, but is not limited to:

- the funder's Terms and Conditions.
- Non-Disclosure Agreements (NDAs) with IMP suppliers and third-party providers to enable discussion about the Protocol.
- Collaboration Agreements.
- Data and Material Transfer Agreements.
- Draft outline NHS model Non-Commercial Site Agreements (mNCA) and Organisation Information Documents (OIDs).

Other key trial agreements may be developed and drafted during Stage 2 of the SAP and will require the input of the CI and appointed CTU (where necessary), these include:

- IMP manufacturing and supply agreements (CTIMPs).
- Laboratory agreements.
- Device supply agreements.
- QP to QP Release Agreements (CTIMPs).

v. drafting of the internal Roles and Responsibilities (Memorandum of Understanding- MoU) document between the Sponsor, CTU and CI/co-CI**.)**. This document establishes which party is responsible for each area of study activity. An MoU is required for all CTIMPs and Medical Device Trials and is recommended for other categories of higher risk studies The MoU must be signed by all parties (including the CI/co-CI, Sponsor and the CTU) prior to the Sponsor issuing Final Sponsor Approval to Commence. The MoU may be reviewed and amended periodically throughout the trial.

vi. review and authorisation of the completed Integrated Research Application System (IRAS) Form. The CI (or their delegate) will lead on the completion of the trial IRAS Form. For the submission of CTIMPs and Medical Device Trials, the Combined IRAS System must be used. Please note that this system requires separate log-in credentials to the standard IRAS and applicants will need to create an NIHR Identity Gateway account. For high risk studies not classed as CTIMPs or Medical Device Trials, the standard IRAS system should be used;

vii. the development of all background essential documents, processes and Standard Operating Procedures (SOPs) necessary to support the management of the trial. Examples of essential documents include, but are not limited to:

- the Case Report Form(s).
- database development and Data Management Plans.
- Study Monitoring Plans.
- Delegation Logs.
- Lab and Pharmacy Manuals.
- Completion of any Vendor Assessments.
- Trial Management Group (TMG) Charters, template Agendas and meeting minutes.
- Independent Data Monitoring Committee (IDMC) Charters, template Agendas and meeting minutes.
- Trial Steering Committee (TSC) Charters, template Agendas and meeting minutes.
- Up to date GCP certificates and CVs for all key study staff.
- any SOPs to detail any CTU processes and study-specific processes.

5.2.2 Issuing of Sponsorship in Principle and Insurance Arrangements for Higher Risk Studies

Upon successful completion of Stage 2, a Sponsorship in Principle letter will be generated by the JRO. The Sponsorship in Principle letter permits the CI to submit the IRAS application to the REC, MHRA and any other approval bodies as required (e.g. the Confidentiality Advisory Group (CAG)). Sponsorship in Principle is granted on the assumption that the study:

- achieves a favourable REC and HRA/HCRW approval (and any other approvals as specified in the Sponsorship in Principle letter, e.g. CAG approval).
- achieves MHRA approval (for CTIMPs and Medical Device Trials).

AND that it is conducted in compliance with:

- the principles of GCP.
- the applicable Regulations (in the case of CTIMPs and Medical Device Trials).
- the UK Policy Framework (as amended).
- the applicable CU and CAVUHB policies and procedures.
- applicable laws and regulations, including but not limited to the Human Tissue Act, the Data Protection Act and the Mental Capacity Act (as amended).

A PDF copy of the letter will be issued to the CI and any other key study team members by email and a copy saved on the electronic Sponsor file. The Sponsorship in Principle letter is the record of Sponsorship, and a copy of this letter should be retained by the CI in the Investigator Site File or the Study Master File.

For CU-Sponsored trials, a trial-specific insurance certificate will be provided with the Sponsorship in Principle letter, and both documents should be uploaded as part of the IRAS application. For CAVUHB-Sponsored trials, NHS clinical indemnity will apply, and no separate insurance certificate is issued.

Following the issuing of the Sponsorship in Principle letter, the CI (or their delegate) may send a request for Sponsorship Authorisation via IRAS.

The Lead Sponsor Reviewer will provide Sponsor authorisation of the IRAS Form (or the Combined Application for CTIMPs and Medical Device Trials) when they are satisfied that the content of the IRAS Form is:

- accurate in accordance with the study documentation (e.g. the Protocol, Participant Information Leaflets and Consent Forms) and the terms of the funding award (where applicable), and.
- written in compliance with the relevant national and University legislation, policies and governance frameworks, as appropriate.

The CI (or their delegate) is then responsible for submitting the authorised IRAS Form.

For CTIMPs and Medical Device Trials, the Sponsorship in Principle letter does not provide approval to commence the trial at NHS sites (see Stage 3).

5.2.3 Information for trials which receive an unfavourable MHRA and/or REC opinion

Where an unfavourable MHRA and/or REC opinion is issued for a study, the CI should arrange a meeting with the JRO and the appointed CTU (where relevant) to discuss the next steps. Options may include:

- a resubmission of the MHRA and REC application, subject to significant amendments to the trial design and management.
- additional pre-clinical work (e.g. toxicology assessments).
- submitting a request for a costed or no-cost extension.

- revision of the study scope and budget.

In circumstances where a study receives an unfavourable opinion and is no longer deemed to be viable, the Director of the JRO may recommend that the study does not progress.

5.3 Stage 3: Trial set-up leading to Final Sponsor Approval to Commence Recruitment (CTIMPs and Medical Device Trials only)

Expected outcomes of Stage 3: all trial set-up procedures will have been completed satisfactorily and verified via a Sponsor Initiation Meeting, enabling the Lead Sponsor to issue Final Sponsor Approval to commence recruitment at NHS sites. The Lead NHS Trial Site will be in a position to issue confirmation of Capacity and Capability approval to commence the trial at site.

Following favourable MHRA and REC approval (in addition to any other required study approvals as listed on the Sponsorship in Principle letter), the final third stage of the SAP may commence. Stage 3 of the SAP normally consists of the following areas of study set-up activity:

i. the establishment of the Trial Master File (TMF) and template Investigator Site File (ISF). Evidence that the TMF is in place and contains the necessary documents will need to be provided prior to Final Sponsor Approval to Commence being issued. This evidence is normally provided in the form of a TMF review sign-off, arranged by the appointed CTU. The relevant JRO Research Governance Team will establish a Sponsor file.
ii. the development and sign-off of the trial database and CRFs/data collection tools (subject to appropriate user testing and in line with the relevant CTU SOP); the completion of all contracts required to open the trial.
iii. the finalisation of all Essential Documents listed in section 5.2 point vii.
iv. in the case of CTIMPs- QP Release Certificates (for IMPs not sourced via Hospital Pharmacy stocks).
v. the finalisation and sign-off of the trial Delegation of Roles and Responsibilities (MoU) between the Sponsor, CI/Co-CIs and CTU.
vi. the finalisation and sign-off of any other essential contracts required in order for the trial to start, as determined by the Sponsor (e.g. Collaboration Agreements, Material Transfer Agreements, Data Sharing Agreements etc.).
vii. the trial management team will have liaised with at least one NHS Trial Site (normally the Lead NHS Trial Site) to finalise site costs and delivery requirements. The Local Information Pack and mNCA required for the Lead NHS Trial Site (NB. only the Lead Trial Site needs to be ready to open to recruitment by the end of Stage 3) should be finalised. The Lead NHS Trial Site should be in a position to issue Capacity and Capability approval. The trial management team may have already completed Site Initiation Visit

(SIV)/Training with the Lead NHS Trial Site, or an SIV can be arranged following the issuing of the Final Sponsor Approval to Commence letter.

Upon successful completion of Stage 3, a Sponsor Initiation Meeting will be arranged between the Lead Sponsor Reviewer and the CI and/or the Trial Manager. A JRO Sponsor Initiation Report will be completed, highlighting any actions required to be completed before Final Sponsor Approval to Commence the trial can be confirmed.

When the Lead Sponsor Reviewer is satisfied that all actions identified during the Sponsor Initiation Meeting have been completed, the Lead Sponsor Reviewer will arrange for the Final Sponsor Approval letter to be issued to the CI (with all key trial contacts copied in).

6.0 SPONSOR GREEN LIGHT TO COMMENCE RECRUITMENT AT AN NHS SITE

Recruitment cannot commence in an NHS organisation or social care setting until Capacity and Capability (C&C) approval has been granted by the relevant NHS organisation (or the equivalent permission to commence has been granted by a social care setting) and the Sponsor has issued the Green Light to commence recruitment at the individual site.

The green light process for higher risk studies which are not CTIMPs or Medical Device Trials will be agreed in the trial MoU, on a per study basis.
Prior to the opening of each study site the template green light checklist (FRM/001/14) must be prepared by the trial management team and agreed with the JRO Governance team, for CTIMPs and Medical Device Trials. For trials where CTUs wish to use their own regulatory green light checklist template, this will have been reviewed during the vendor assessment process at the start of the study to confirm it meets Sponsor requirements.

For multi-centre studies under CTU management, the CTU's green light processes may be followed, with the agreement of the Sponsor.

The documents which accompany a green light request will be agreed by the JRO Sponsor Lead at the same time as the Green Light checklist is completed. At a minimum this will include the signed and dated CV and GCP of the PI and the Site Initiation Visit (SIV) Report with an accompanying confirmation that all actions identified have been completed.

7.0 DURATION OF SPONSORSHIP

Sponsorship is considered to apply for the duration of the study until the study is archived, subject to adequate monitoring and audit performance and providing the following approvals are maintained by the CI (or their delegates):

- a valid favourable MHRA and/or REC opinion. Valid regulatory and ethics approvals must be maintained by the CI (or their delegate) for the duration of the study. Approvals are considered maintained as long as the study is conducted in line with the agreed study documents and the conditions of the MHRA and/or REC approvals and the Sponsorship Approval.
- the submission of an annual Development Safety Update Report (DSUR) to the MHRA (for CTIMPs and Medical Device Trials). The CI or CTU is responsible for the coordination and submission of the DSUR.
- a valid HRA/HCRW Approval.
- continued support for the study from the NHS/social care site organisation(s)- provided through the confirmation of C&C.
- all other study approvals (as listed on the Sponsorship in Principle or Final Sponsor Approval to Commence letter) are maintained as appropriate (e.g. CAG, ARSAC approvals).
- all changes and updates to the study are formally recorded via the HRA Amendment process and approved by the relevant Sponsor organisation;
- there is adequate funding and resource in place to support the study, or the CI is able to confirm that additional support can be sourced (e.g. via additional funding, staffing support or extensions to funding arrangements).
- all eligible safety events/ adverse incidents for devices have been properly recorded and reported to the Sponsor, regulators (where relevant) and REC.
- all potential serious breaches are properly recorded and reported to the Sponsor and regulators.

If modifications to the study or study documentation are required, the JRO Research Governance team will liaise with the CI (or their delegate) to discuss and review the required changes. The process for the review and approval of modifications is covered in the SOP Managing Modifications for JRO Sponsored Research.

8.0 RIGHT TO WITHDRAW SPONSORSHIP

CAVUHB and CU reserve the right to withdraw Sponsorship as a result of significant monitoring or audit findings, or where there are significant concerns around participant safety, CI oversight, the management and/or conduct of a study.

9.0 ASSOCIATED DOCUMENTATION

SOP/001/04 SOP for Applying for Sponsorship- Low and Medium Risk Studies for JRO Sponsored Research.
SOP/003/03 SOP Managing Modifications for JRO Sponsored Research.
SOP/001/03 Capacity and Capability SOP (UHB 448)

FRM/001/13 JRO Sponsorship Request Form
FRM/001/14 JRO Green Light Checklist
FRM/010/01 JRO Sponsor Initiation Report
TPL/001/10 JRO Template Delegation of Roles and Responsibilities- CTIMPs and Medical Device Trials

Appendix 1: Applying for Sponsorship Process Flowchart- Higher Risk Studies