University College London Hospitals
NHS Foundation Trust

Approval of hosted clinical trials using Investigational Medicinal Products (IMPs) which are considered to be Genetically Modified Organisms

UCLH policy

Policy number	048/CLN/T
Issue number	5
Issue date	23/04/2021
Approved by	Policy Approval Sub Group
Responsible Director	Director of Research
Policy Author	JRO QA Manager
Review Body	UCLH/UCL Joint Research Office, UCL Biological Safety Advisor (on behalf of UCL GMSC), UCLH Acting Director for Infection Prevention and Control
Documents to read in conjunction with this policy	UCLH/UCL Joint Research Office Standard Operating Procedure for the Risk Assessment process for clinical trials involving genetically modified organisms (GMO).
Complete review by date	31/03/2024

If reading a printed copy, always check that it is the most recent approved version. This can be found on the Policies page on the staff intranet (myUCLH).

List of reviewers & contributors *Include here whether Counter Fraud; Infection Control Team or Interserve Facilities Management (IFM) were asked to review the policy and if comments were received*	Research Quality & Safety Manager (Joint Research Office) Head of Research Governance and Compliance (Joint Research Office) Advanced Therapy Regulatory Managers (Joint Research Office) UCL Biological Safety Advisor and UCL Genetic Modification Safety Committee (GMSC) representative Acting Director of Infection Prevention and Control (UCLH DIPC)	
Summary of main points from consultation	Major changes to the process for submitting and reviewing GM risk assessments via the UCLH Director of Infection, Prevention and Control (DIPC) and UCL GMSC have been made. Previous chair of UCL/UCLH GMSC, stepped down and with no new Chair identified, the committee was no longer viable. The main UCL GMSC was approached and a new process agreed with them. UCLH/UCL Joint Research Office (JRO) have issued a new Standard Operating Procedure for the Risk Assessment process for clinical trials involving genetically modified organisms (GMO). This policy has therefore been revised to include details of the new process.	
Review body *Author to complete*	JRO-UCL GMSC Group	Date of meeting when policy reviewed and endorsed: 03/02/2021
Date of meeting when policy approved by PASG	Approved 20th April 2021*, subject to required changes (which have been made)*	

Review amendment log – *must be completed each time the policy is revised*

Version No	Date amendments made	Description of change
5	April 2021	Major updates – previous GMSC has been discontinued, therefore a new process for reviewing GMO-IMP trial risk assessments has been put in place with the UCLH DIPC and UCL GMSC (via the JRO). Policy has been re-written to reflect this, with reference to a new JRO Standard Operating Procedure for Risk Assessment process for clinical trials involving genetically modified organisms (GMO), which includes the detailed instructions UCLH Principal Investigators must now

		follow.
4	24/07/2019	Minor updates only – grammatical changes and graphical reformatting. Updated to the current UCLH Policy template. Update contact details and committee membership.
3	31 May 2016	Minor updates only – grammatical changes and changes to job titles. Reference to additional GCP guidance document 'European Commission Guidance: Detailed guidelines on good clinical practice specific to advanced therapy medicinal Products'. Updated UCLH pharmacy contact from Rita Gupta to Chi Chung.

Environmental

Do you really need to print this document? Please consider the environment before you print this document and where possible copies should be printed double-sided. Please also consider setting the Page range in the Print properties to avoid printing the policy in its entirety.

Table of contents **Page Numbers**

1. Summary

This policy sets out the University College London Hospitals NHS Foundation Trust (UCLH) requirements for approval of hosted Clinical Trials which use an investigational medicinal product (IMP) considered to be a genetically modified organism (GMO). These are included but not limited to genetically modified viral vaccines or some gene therapy medicinal products, including genetically modified cells and viral vectors. These will be referred to as GMO-IMPs throughout this policy.

2. Equality Impact Statement

The author of this policy has undertaken an Equality Impact Assessment (EIA) and has concluded that there is no negative impact on any of the protected equalities groups. The completed EIA form is available from the Policy Compliance Officer.

3. Introduction

The use of an investigational medicinal products (IMP) considered to be a genetically modified organism (GMO) in a clinical trial, is subject to a risk assessment process that meets the requirements of GMO legislation.[1] This is to ensure any potential direct or indirect risk to human health or the environment is identified and appropriate mitigation strategies are implemented. There is a defined classification system based on the use of the GMO as either contained use or deliberate release[2]. For contained use, the classification system has four classes of activity, with differing requirements as the risk increases.

It is anticipated that the use of GMO-IMPs on University College London Hospitals NHS Foundation Trust (UCLH) premises will fall under Class 1 contained use activity[3] and will include some Advanced Therapy Investigational Medicinal Products (ATIMP) trials and gene therapy medicinal product (GTMP) trials involving hospital patients or healthy volunteers. It is the responsibility of the Sponsor to determine the type and classification of the use of the GMO, as some activities may be considered Class 2.

The product and patient safety aspects of GMO-IMP trials are regulated under the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended). The protection of human health and the environment from these products is regulated under the Genetically Modified Organisms (Contained Use) Regulations (2000) as amended by Genetically Modified Organisms (Contained Use) (Amendment) Regulations in 2002, 2005, 2010 and 2014.

There are four levels of containment identified in the latter regulations with Level 1 being considered the lowest risk and Level 4 the highest risk. Whichever containment level is deemed appropriate effectively sets the class of the activity that in turn determines the notification requirements.

[1] https://www.hse.gov.uk/biosafety/gmo/law.htm
[2] Deliberate Release: https://www.hse.gov.uk/biosafety/gmo/law.htm
[3] The Genetically Modified Organisms (Contained Use) Regulations 2014

Most clinical trials of GMOs fall under The Genetically Modified Organisms (Contained Use) Regulations 2014. Most trials are considered Class 1 GMO activities (low risk). The Health and Safety Executive (HSE) Scientific Advisory Committee on Genetic Modification (SACGM) advises that IMPs classified as Class 1 represent no or negligible risk to human health and the environment and require only routine clinical practices to reduce infectivity [4]. IMPs classified as Class 2 represent low potential hazard to personnel and the environment, and although the containment requirements are not significantly greater than those for Class 1, staff handling such products must be appropriately trained to avoid exposing either themselves or others[1]. The regulations require that the **organisation responsible for the contained use** (e.g. the NHS Trust where GMO trial is carried out) obtain advice on the risk assessment from a GMSC (mandatory for class 2 and above) OR a competent individual (acceptable for Class 1 only) with expertise in risk assessment relating to contained use (e.g. Biological Safety Officer/Advisor).

GMO-IMPs classified as Class 3 or Class 4 will not be approved to be conducted at UCLH.

The HSE needs to be notified when a premises uses a GMO for the first time. UCLH has notified the HSE of its use of Class 1 GMOs (notification date; 28/01/2009). UCLH's GM Centre Number is 3048, and further details can be located on the HSE GMO Public Register[5]

UCLH premises included on this notification:

- National Hospital for Neurology and Neurosurgery (NHNN), Queen Square, WC1N 3BG
- The Wolfson Cellular and Gene Therapy Unit, Chenies Mews, WC1E 6HX
- University College Hospital, 235 Euston Road, NW1, 2BU
- Macmillan Cancer Centre, Huntley Street, WC1E 6AG

For subsequent Class 1 activity, no further HSE notification is required under the Contained Use regulations for Class 1 activities. However, additional notification is required for any subsequent contained uses of Class 2 GMO as a different level of stringency will apply. The process for notification will need to be determined by the UCLH/UCL Joint Research Office (JRO) and the UCLH IPC team. Any activities considered to be Class 2 must therefore be discussed with the JRO in the first instance, prior to study reviews and UCLH Confirmation of Capacity and Capability.

UCLH premises not included on the HSE GMO Public Register

The above premises are authorised for GMO activity, per notification to the HSE. If the investigator's GMO-IMP trial will be handled/administered on UCLH premises not listed above, please contact the JRO QA Manager and UCLH DIPC in the first instance, as notification to HSE will be required.

[4] *Scientific Advisory Committee on Genetic Modification. Part 6. Guidance on the use of genetically modified micorganisms in a clinical setting. HSE* http://www.hse.gov.uk/biosafety/gmo/acgm/acgmcomp/

[5] HSE GMO Public Register: https://www.hse.gov.uk/biosafety/gmo/notifications/publicregister.htm

The JRO has an agreed process in place with the UCL Genetic Modifications Safety Committee (GMSC) and the UCLH Infection, Prevention and Control (IPC) team to facilitate the review and approval of Class 1 GMO-IMP trials conducted on UCLH premises. This process utilises the existing GMO systems, expertise, and experience of both organisations to facilitate the safe and compliant conduct of clinical trials using GMO-IMPs.

Policy exclusions:

- This policy does not apply to activities classified as deliberate release (the intentional release of GMOs into the environment) where different regulations and requirements apply. In the UK, most GMO clinical trials are considered contained use.
- This policy does not apply to licensed ATIMP activities involving GMOs (non-research) or the procurement and authorisation process for ATIMPs; please refer to the *Use of Advanced Therapy Medicinal Products Policy*

4. Objectives

4.1. To ensure that UCLH receives expert advice on the risk of infection from particular GMO-IMPs.

4.2. To ensure that trials using GMO-IMPs are conducted in compliance with the required regulations and managed in a way to reduce risks of infectivity to patient, staff, and public and environment.

5. Scope

This policy applies to the risk assessment of the GMO-IMP handling, preparation, administration, and disposal during clinical use. It does not apply to the production and manufacturing activity of a GMO-IMP. The risk assessment for production and manufacturing should be carried out in accordance with the Sponsor or manufacturers procedures.

The policy applies to all commercial and non-commercial clinical trials involving IMPs considered to be GMOs (GMO-IMPs), which will be administered to UCLH patients or handled and administered on UCLH premises. All staff members who are involved in the approval and conduct of such clinical trials must be aware of this policy and the related *JRO SOP for Risk Assessment process for clinical trials involving genetically modified organisms (GMO)*, along with the responsibilities and requirements specified throughout.

The risk assessment process for GMOs detailed within this SOP is separate from:

- Sponsorship authorisation
- Clinical trial applications to the Medicines and Healthcare products Regulatory Agency (MHRA), Health Research Authority (HRA) and Research Ethics Committees (REC)
- NHS research site Confirmation of Capacity and Capability.

All authorisations and GMO-IMP risk assessment approval(s) must be in place prior to initiating these types of clinical trials.

This policy sets out the UCLH/UCL Joint Research Office (JRO) requirements for submission and approval of risk assessments for clinical trials which use a GMO-IMP for Class I contained use. These will be referred to as GMO-IMPs throughout this policy.

For any other class of activity on UCL/UCLH premises, the investigator must contact the JRO before proceeding with their risk assessment.

6. Definitions

Advanced Therapy Medicinal Product (ATMP)/ Advanced Therapy Investigational Medicinal Product (ATIMP)	Means any of the following medicinal products for human use: a gene therapy medicinal product, a somatic cell therapy medicinal product, or a tissue engineered product. If they are being tested in a clinical trial they are referred to as ATIMPs.
Contained Use (CU):	Any activity in which organisms are genetically modified or in which such GMOs are cultured, stored, transported, destroyed, disposed of or used in any other way, and for which physical, chemical or biological barriers, or any combination of such barriers, are used to limit their contact with, and to provide a high level of protection for, humans and the environment Further information here.
Gene therapy medicinal product	A gene therapy medicinal product is a biological medicinal product which has the following characteristics: (a) It contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding, or deleting a genetic sequence; and (b) Its therapeutic, prophylactic, or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence Vaccines for infectious diseases are excluded from the definition (per the Human Medicines (Amendment etc.) (EU Exit) Regulations 2019). A Gene Therapy Medicinal Product may be classed as a GMO,

	for example recombinant viral vectors.
Genetically modified organism (GMO)	An organism (with the exception of humans) in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination (further information here).
Genetically modified microorganisms (GMM)	GMMs are a category of GMOs, which includes bacteria, viruses parasites and fungi.
Investigator's Brochure (IB)	The IB is a compilation of the clinical and non-clinical data on the IMP(s) that are relevant to the study of the product(s) in human participants (ICH GCP E6 (R2), Section 7.1).
Investigational Medicinal Product (IMP)	A pharmaceutical form of an active substance or placebo being tested, or to be tested, or used, or to be used, as a reference in a clinical trial, and includes a medicinal product which has a marketing authorisation but is, for the purposes of the trial: (a) used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorization, (b) used for an indication not included in the summary of product characteristics under the authorisation for that product, or (c) used to gain further information about the form of that product as authorised under the authorisation (Medicinal Products for Human Use (Clinical Trials) Regulations 2004 as amended).
Investigational Medicinal Product Dossier (IMPD)	The IMPD includes summaries of information related to the quality, manufacture and control of any IMP (including reference product and placebo), and data from non-clinical and clinical studies (further information here).
Organism	Any biological entity capable of replication or of transferring genetic material.
Principal Investigator (PI)	The PI is responsible for the conduct of a clinical trial at a research site (e.g. UCLH). If a trial is conducted by a team of individuals at the trial site, the PI is the leader responsible for the team.
Standard Operating Procedure (SOP)	Detailed, written instructions to achieve uniformity of the performance of a specific function.
Sponsor	The organisation who, under the Medicines for Human Use (Clinical Trial) Regulations 2004 takes responsibility for initiating, management and financing of the trial. Sponsors may be academic institutions or charities (e.g. non-commercial) or pharmaceutical or industry companies (e.g. commercial)..

7. Duties and responsibilities

	Responsible Person	Summary of duties
1	JRO Quality Assurance Manager (or delegate) **(JRO QA)**	- First point of contact for UCL/UCLH GMO-IMP risk assessment queries/submissions - Responsible for coordinating GM reviews and approvals for clinical trial activity within UCLH - Provides JRO GM templates and process; advises on submission and approval process - Coordinates UCLH IPC review and approval (where applicable) - Advises on UCL RiskNet submission process - JRO/UCLH 'Approver' on UCL RiskNet - Provides summary of GMO-IMP clinical research activity to UCL GMSC and relevant JRO Committees (e.g. Clinical Research Governance Committee)
	UCL Biological Safety Advisor **(UBSA)**	- Additional 'Approver' for UCL RiskNet Class 1 GM risk assessment submissions - Provides expert advice on GMO-IMP classifications and regulatory requirements (via MoU with UCLH) - Principal liaison with the UCL GMSC - Advises on UCL RiskNet submission process - Recommend any specific risk control measures that need to be put in place to protect patients, staff and public in the conduct of the trial and the appropriate arrangements for receipt, storage, preparation and handling, transportation, disposal and spillage of the GMO-IMP.
	UCL Genetic Modification Safety Committee **(UCL GMSC)**	- To act as the Genetic Modification Safety Committee as required by Regulation 8 of the Genetically Modified Organisms (Contained Use) Regulations 2014 (refer to UCL GMSC Terms of Reference here) - Provide advice on GM risk assessments prepared by partner trusts (e.g. the Anthony Nolan Research Institute and The Royal Free London NHS Foundation Trust) in accordance with local written arrangements and MoUs - Recommend any specific safety measures that need to be put in place to protect patients, staff and public in the conduct of the trial and the appropriate arrangements for receipt, storage, preparation and handling, transportation, disposal and spillage of the GMO-IMP.

	Principal Investigator (hosted trials), or suitable delegate **(PI)**	- Completing and submitting the UCL/JRO risk assessment forms, study protocol, IB, IMPD (if available) to the relevant groups (e.g. JRO/UCL GMSC or NHS IPC/Biosafety Lead), in consultation with the Sponsor (and Pharmacy where applicable) and in accordance with this SOP. - Ensure all staff have the appropriate training to undertake work with GMOs including the receipt, onsite storage, onsite preparation and handling, onsite transportation, administration, and disposal of GMO-IMP in line with GCP. This training should be documented in the Investigator Site File and the individuals named on the trial delegation log. - Ensure procedures and resources are in place to safeguard against known and potential hazards as identified by the GM risk assessment for the study - Ensure that requirements from the GMSC and DIPC are in place before the trial is opened (e.g. SOPs, safety measures, etc.) - Notify the Pharmacy Clinical Trial Lead about the trial as early as possible, provide associated documentation required by pharmacy and discuss to ensure compliance with Good Clinical Practice (GCP) aspects of medicines management.

	UCLH Director of Infection, Prevention and Control (**DIPC**)	The DIPC at an NHS Trust undertakes a similar role as a Biological Safety Officer and is the first reviewer of GMO-IMP risk assessment documents. They advise on matters of safety and assists the clinical trial teams in undertaking the actions required to comply with statutory obligations. **Prior to UCL GMSC approval**, reviews the GM Clinical Use Risk Assessment Form (Section 10), protocol, IB, relevant trial specific SOPs (if applicable), and will respond with one of the following: - That adequate measures have been considered and/or arranged (includes handling, use and disposal of the product within the trust), and approval has been issued - That further risk reduction measures need to be put in place, and an updated GM Clinical Use Risk Assessment Form needs to be resubmitted for further review prior to DIPC approval - That the trial should not take place at UCLH (and subsequent UCL GMSC review and Confirmation of Capacity & Capability is no longer applicable).
	Health and Safety Executive **(HSE)**	HSE operates and enforces legislation in Great Britain that aims to control the risks to human health and the environment arising from activities involving GMOs in containment under the Genetically Modified Organisms (Contained Use) Regulations 2014.
	UCLH/UCL Joint Research Office **(JRO)**	The JRO supports the set up and development of the clinical research portfolio of UCL and UCLH, and provides Sponsorship, UCLH Confirmation of Capacity & Capability, and research management support to a network of local trusts associated with UCL and UCLH.
	UCLH Pharmacy Clinical Trials Lead (or delegate within Pharmacy Clinical Trials Team)	The UCLH Pharmacy Clinical Trial lead will: - Work with the PI (and others where relevant) to ensure that the on-site arrangements for receiving, handling, storage and destruction of the GMO-IMP will be in compliance with GCP. - Ensure that suitable arrangements for dispensing will be in place at site, if applicable. Ensure that suitable arrangements will be in place for transportation from on-site storage or on-site preparation to administration area, and that storage in the administration area, if applicable, is compliant with the requirements of GCP.

8. Procedure for submitting GM Class 1 Risk Assessments

The PI intending to carry out any contained use activity with GMO-IMPs, must assess the risks to human health and the environment by performing the following tasks:

1. Completing the GM Clinical Use Risk Assessment Form and obtaining UCLH DIPC approval

Prior to UCL GMSC approval, the DIPC is responsible for reviewing the GM Clinical Use Risk Assessment Form, protocol, IB, relevant trial specific SOPs (if applicable), and will respond with one of the following:

- That adequate measures have been considered and/or arranged (includes handling, use and disposal of the product within the trust), and approval has been issued
- That further risk reduction measures need to be put in place, and an updated GM Clinical Use Risk Assessment Form needs to be resubmitted for further review prior to DIPC approval
- That the trial should not take place at UCLH (and subsequent UCL GMSC review and Confirmation of Capacity & Capability is no longer applicable).

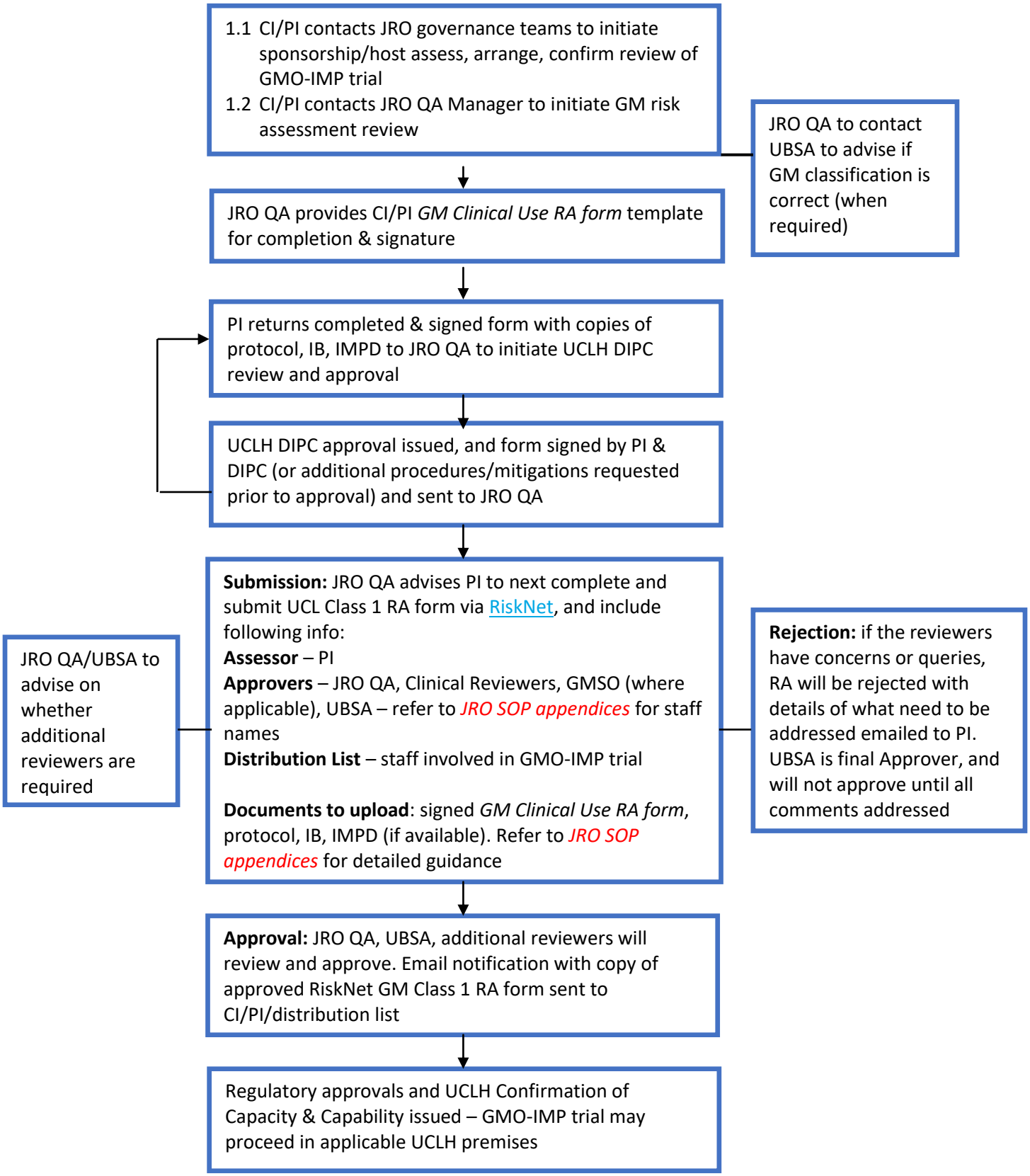
2. Making a Class I GM Risk Assessment submission on the UCL GMSC online risk assessment tool in riskNET and uploading the GM Clinical Use Risk Assessment Form and relevant study documents.

The forms should be completed with sufficient detail regarding the potential hazards, and be understandable by those not familiar with the research area or GMO-IMP.

PIs must follow the *JRO Standard Operating Procedure for Risk Assessment process for clinical trials involving genetically modified organisms (GMO),* which details the process for submitting GM Class 1 risk assessments and obtaining GMSC approval.

All the above approvals must be in place prior to initiating any GMO activities at UCLH.

Class 1 GMO-IMP Activity – submission and approval process



Relevant Contacts

Refer to the *JRO Standard Operating Procedure for Risk Assessment process for clinical trials involving genetically modified organisms (GMO)* (available on the JRO SOP webpage) and related appendices for relevant contacts (including JRO Quality Assurance Team, UCL GMSC, etc.).

Changes following initial GMSC approval

Substantial amendments or changes to GMO-IMP trial

Following the initial GMSC approval, a clinical trial may undergo amendments or changes affecting the conditions of DIPC and GMSC approval (e.g. amendments to ATIMP administration, preparation instructions, etc.). New risk assessment forms will need to be submitted for approval, highlighting the changes. The process outlined within the *JRO SOP* will need to be repeated (or followed for the first time) for the trial. If you are unsure, please contact the JRO QA Manager to discuss.

Change of PI (Assessor) and Approvers

If the PI has changed, the JRO QA Manager will need to be informed to ensure future notifications regarding the GMSC approval are directed appropriately (via riskNET).

Similarly, if there have been any changes to the Approvers, contact the JRO QA team to identify a suitable replacement.

9. Dissemination & Communication

The policy will be accessible on myUCLH and the JRO website. The policy will be made available to relevant research departments and Principal Investigators within UCLH.

10. Monitoring and Audit

What in the policy is going to be monitored	Monitoring method	Who will lead the monitoring?	How often?	Where will it be reported?
UCLH GM risk assessment processes (i.e. ensuring applicable GM authorisations were in place for GMO-IMP trials approved at UCLH)	Monitoring checks	JRO QA Manager	Annually	Clinical Research Board

11. References

European Commission's definition of a GMO ("*Question and Answers on the regulation of GMOs in the EU")*
European Investigational Medicinal Products Dossiers
European Medicines Agency: Advanced therapy medicinal products: overview
Genetically Modified Organisms (Deliberate Release) Regulations 2002
The Genetically Modified Organisms (Contained Use) Regulations 2014
The Human Medicines (Amendment etc.) (EU Exit) Regulations 2019
HSE GMO Public Register
HSE GMO Regulations (contained use)
ICH E6 (R2) Good clinical practice
Medicinal Products for Human Use (Clinical Trials) Regulations 2004 as amended
UCL Genetic Modifications Safety Committee (GMSC)
UK Policy Framework for Health and Social Care Research

12. Appendices

Appendix 1: GM Clinical Use Risk Assessment form (template available via myUCLH and JRO website SOPs and Templates pages)

Appendix 2: UCL Class 1 GM Risk Assessment Form (accessible via UCL riskNET)