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Approval of Gene Therapy Medicinal Products (GTMP) and Gene Therapy Investigational Medicinal Products (GTIMP) Procedure

Introduction and Aim

This document is supporting the following policy
Approval of Gene Therapy Medicinal Products (GTMP) and Gene Therapy Investigational Medicinal Products (GTIMP) Policy

It will achieve safe use of GTMPs and GTIMPs

Objectives

- Approval for use and safe management including compliance with relevant regulations
- Appropriate HSE notification
- Review of all licenced and unlicensed GTMP as well as use of GTMPs in trials by the GMSC
- Clarification of roles and responsibilities of those involved in the delivery of GTMPs/GTIMPs
- Explain how advice on the risk of infection from genetically modified organisms (GMOs) is provided and any risks (to patients, staff, public and environment) are minimised

Scope

This procedure applies to all of our staff in all locations including those with honorary contracts.

Equality and Health Impact Assessment	*An Equality and Health Impact Assessment (EHIA) has been completed and this found there to be no impact*
Documents to read alongside this Procedure	• GTMP & GTIMP Policy • Handling gene therapy medicinal products SOP • C&V UHB Risk assessment for proposed activities involving Gene Therapy Medicinal Products (GTMP) or Gene Therapy Investigational Medicinal Products (GTIMPs) • Pan UK PWG for ATMPs – Gene Therapy Governance and Preparation
Approved by	Genetic Modification Safety Committee (GMSC) Quality Safety and Experience Committee

Accountable Executive or Clinical Board Director	Executive Medical Director
Author(s)	Consultant Pharmacist Advanced Therapy Medicinal Products and Haematology

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	*27.12.21 Via QSE Committee Chair*	*23.12.2021*	*New Document*

1. Introduction

This procedure sets out the requirements for CAVUHB approval of

a) Clinical Trials which use an investigational medicinal product (IMP) designated as a genetically modified organism (GMO) (also known as GTIMPs).
b) the therapeutic use of Gene Therapy Medicinal products (GTMPs) including off-licence use outside of clinical trials.

The following legislation should be consulted. GTIMPs are regulated by the MHRA and HSE. Licensed GTMPs are governed by the medicines regulators only.

Table 1 GTMP legislation and guidance documentation

Human Medicines Regulations 2012 SI: 2012 - No. 1916
Regulation (EC) NO 1394/2007 On Advanced Therapy Medicinal Products ("The ATMP Regulation")
Health and Safety Executive (HSE) Genetically Modified Organisms (Contained Use) Regulations 2014
The Medicines for Human Use (Clinical Trials) Regulations 2004
If the gene therapy product is being used in a clinical trial reference should be made to the following :-
Clinical Trials Directive 2001/20/EC
Medicines for Human Use (Clinical Trials) 2004 SI: 2004- No.1031 as amended

Classification and Containment Levels for GTMPs

There are four classes of activities according to the regulations. The classification is based on the level of risk to humans and the environment.

Class 1 – activity of no or negligible risk for which containment level 1 is appropriate to protect human health and the environment

Class 2 – activity of low risk for which containment level 2 is appropriate to protect human health and the environment

Class 3 – activity of moderate risk for which containment level 3 is appropriate to protect human health and the environment

Class 4 – activity of high risk for which containment level 4 is appropriate to protect human health and the environment

The classification of the activity involving the genetically modified organism (GMO) is determined by the containment and control measures identified as necessary via the risk assessment. Containment measures are detailed in Schedule 8 of the Genetically Modified Organisms (Contained Use) Regulations 2014 available at:

http://www.hse.gov.uk/pubns/priced/l29.pdf

Most activities involving GTMPs that are currently in clinical trials and in development will be class 1 or 2.

For example: Containment level 1 is suitable for class 1 activities involving GTMPs such as replication incompetent adeno-associated viruses. Containment level 2 is required for class 2 activities such as the use of conditionally replicating virus vectors. However, the classification for each individual activity must be determined by the risk assessment process that identifies necessary control measures from Schedule 8. Control measures identified from the highest containment level determine the class of the activity. For further details on risk assessment of GMOs see the HSE Compendium of guidance Part 2: http://www.hse.gov.uk/biosafety/GMO/acgm/acgmcomp/part2.pdf

This procedure deals with Class 1 and Class 2 activities, involving GTIMPs and GTMPs.

GTMPs classified as Class 3 represent moderate risk and Class 4 high risk to human health and the environment. Investigators wishing to undertake a Clinical Trial involving a Class 3 GMO must contact the chair of the Genetic Modification Safety Committee at the earliest opportunity to discuss the feasibility of the proposed Trial. CAVUHB will not use Class 4 GMOs.

Staff handling GTMPs or GTIMPs must be appropriately trained to avoid exposing either themselves or others to risk.

2. Glossary

BSO	Biological Safety Officer is a specialist adviser on matters relating to safe handling of biological materials. The BSO advises the GMSC on matters of safety and reviews recommendations and requirements from the GMSC. The BSO assists the clinical trial teams in undertaking the actions required to comply with statutory obligations.
Gene therapy medicinal product (GTMP)	A gene therapy medicinal product is defined as 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; (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.
Gene therapy investigational medicinal product (GTIMP)	A GTMP (see above) which falls under the classification of an Investigational medicinal product (IMP) in a clinical trial.
GCP	Good Clinical Practice (GCP) is an international quality standard that is provided by International Conference on Harmonisation (ICH), an international body that defines standards, which governments can transpose into regulations for clinical trials involving human subjects. See also the European Commission Guidance: Detailed guidelines on good clinical practice specific to advanced therapy medicinal products (ENTR/F/2/SF/dn D(2009) 35810)

GMO	Genetically modified organism. 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' using 'recombinant nucleic acid techniques involving the formation of new combinations of genetic material by the insertion of nucleic acid molecules, produced by whatever means outside an organism, into any virus, bacterial plasmid or other vector system and their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation.
GMO - IMP	Genetically modified organisms which fall under the classification of an Investigational Medicinal Product (IMP) in a clinical trial. These can be genetically modified viral vaccines and some gene therapy medicinal products including viral vectors and cells genetically modified by viral vectors.
GMM	Genetically modified microorganisms GMMs are a category of GMOs which includes bacteria, viruses, parasites and fungi.
GMSC	Genetic Modification Safety Committee, a committee that is mandated by the Health & Safety executive and reports to the UHB Quality Safety and Experience Committee, it risk assesses and approves use of gene therapy medicinal products and gene therapy investigational medicinal products in the Health Board.
HSE	Health and Safety Executive HSE is Great Britain's independent regulator for work-related health, safety and illness. It operates and enforces legislation 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.
IB	Investigator's Brochure 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 subjects

IMP	Investigational Medicinal Product: a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form
IMPD	Investigational Medicinal Product Dossier The IMPD includes information related to the quality, manufacture and control of the Investigational Medicinal Product.
MHRA	The Medicines and Healthcare products Regulatory Agency (MHRA) is the UK government agency which is responsible for ensuring that medicines and medical devices work and are acceptably safe. They regulate clinical trials of medicines and ensure compliance with statutory obligations.
PI	Principal Investigator. The PI is responsible for the conduct of a clinical trial at a trial site.
R&D Office	The R&D Office supports the development of the clinical research portfolio of Cardiff & Vale UHB and provides research management support.
SOP	Standard Operating Procedure 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 commercial companies.
The Regulations	Genetically Modified Organisms (Contained Use) Regulations (2000) as amended.

3. HSE notification

HSE notification is required to use gene therapy in trials, for further details please refer to Pan UK PWG for ATMPs – Gene Therapy Governance and Preparation Requirements (available from www.sps.nhs.uk https://www.sps.nhs.uk/articles/requirements-for-governance-preparation-of-gene-therapy-pan-uk-pharmacy-working-group-for-atmps/) or HSE website.

Conduct of Clinical Trials involving GTIMPs requires C&V UHB to:

3.1. Notify the HSE of its intention to carry out clinical trials using GTIMPs

- C&V UHB was notified to the HSE for the first time on 11 March 2010.
- HSE GM centre number for C&V UHB is GM754.
- For Class 1 activities, no further permission is required after the first notification

3.2. Prior to the commencement of any related work, notify the HSE of its intention to undertake trial activities involving Class 2 GTIMPs:

- The activity must be notified to the HSE though submission of the 'CU2 - Notification of intention to conduct individual contained uses' form (available on the HSE website https://www.hse.gov.uk/forms/genetic), the C&V UHB Risk assessment for proposed activities involving Gene Therapy Medicinal Products (GTMP) or Gene Therapy Investigational Medicinal Products (GTIMPs) and appropriate fee.

- Since C&V UHB have already notified HSE of class 2 activity any further class 2 activity can commence after HSE acknowledge receipt of notification without further waiting

3.3. Receive advice from the Genetic Modification Safety Committee (GMSC) as to the level of risk related to specific GTMP/GTIMPs.

3.4. Implement any specific measures required to mitigate the risk of infectivity from such GTMPs/GTIMPs, as advised by GMSC.

4. Duties and responsibilities

4.1 C&V UHB Genetic Modification Safety Committee (GMSC)

The committee is a subcommittee of the C&V UHB Quality Safety & Experience Committee (QS&E). Its membership and terms of reference are available on request. The committee will:

4.1.1 Ensure that the HSE is appropriately notified of C&V UHB activities relating to clinical trials of GTIMPs. The GMSC will liaise with the R&D office to ensure appropriate review of the C&V UHB Risk assessment for proposed activities involving Gene Therapy Medicinal Products (GTMP) or Gene Therapy Investigational Medicinal Products (GTIMPs) and CU2 form prior to submission to the HSE, and will review the acknowledgement on receipt.

4.1.2 Review the protocol, the C&V UHB Risk assessment for proposed activities involving Gene Therapy Medicinal Products (GTMP) or Gene Therapy Investigational Medicinal Products (GTIMPs) (associated document) and other relevant trial documentation.

4.1.3 Provide the UHB and the Sponsor with a written risk assessment about the Class of GTMP/GTIMP and its potential level of infectivity.

4.1.4 Decide if proposed investigational or therapeutic use of GMO may safely be undertaken within the UHB and communicate this decision to all relevant parties.

4.1.5 Recommend specific safety measures necessary to protect patients, staff, public and the environment and ensure appropriate arrangements are detailed for receipt, storage, preparation and handling, transportation, disposal and spillage of the GTMP/GTIMP.

4.1.6 The GMSC will confirm one of the following:

a. that adequate measures have been considered and/or arranged (includes handling, use and disposal of the product within the UHB) for the Trial or non-trial use to commence

b. that further risk reduction measures need to be put in place before the trial or non-trial use can commence at C&V UHB

c. that the trial or non-trial use is not approved (should not take place) at C&V UHB

The Chair of the GMSC should also notify the QS&E of the committee's decision.

4.2 R&D office will:

4.2.1 Ensure that the HSE is appropriately notified of C&V UHB activities relating to clinical trials of GTIMPs. The R&D office will coordinate GMSC review, and submission to the HSE of the C&V UHB Risk assessment for proposed activities involving Gene Therapy Medicinal Products (GTMP) or Gene Therapy Investigational Medicinal Products (GTIMPs) and CU2 form for any class 2 or 3 activities proposed to take place in the UHB. The R&D office will ensure receipt and appropriate communication of acknowledgement from the HSE.

4.2.2 Notify the Principal Investigator and/or trial sponsor of this procedure and provide the C&V UHB Risk assessment for proposed activities involving Gene Therapy Medicinal Products (GTMP) or Gene Therapy Investigational Medicinal Products (GTIMPs) to be completed.

4.2.3 Provide advice and assistance to PIs and/or Sponsors on the risk assessment and approval process in line with this procedure.

4.2.4 Before NHS permission is granted ensure that:

a. the GMSC has reviewed and approved the GMSC risk assessment and documentation has been archived by the secretary.

b. Pharmacy is informed about the trial and satisfied that appropriate arrangements (as applicable for the trial) for receipt, onsite storage, onsite preparation and handling, onsite transportation, and disposal of GTIMP, in line with GCP, will be in place prior to the commencement of the trial.

4.4 Principal Investigator (or Clinical Director for off trial use) will:

4.4.1 Complete the Risk assessment of proposed activities involving Gene Therapy Medicinal Products (GTMPs) or Gene Therapy Investigational Medicinal Products (GTIMPs) in consultation with the Sponsor.

4.4.2 Ensure the C&V UHB Risk assessment for proposed activities involving Gene Therapy Medicinal Products (GTMP) or Gene Therapy Investigational Medicinal Products (GTIMPs), protocol, IB and IMPD (if available) are submitted to the GMSC for review.

4.4.3 Ensure the C&V UHB Risk assessment for proposed activities involving Gene Therapy Medicinal Products (GTMP) or Gene Therapy Investigational Medicinal Products (GTIMPs), GMSC approval letter, protocol and any other required documents are submitted to the QS&E Committee following GMSC approval.

4.4.4 Prepare the notification to the HSE if required, which is submitted by the R&D office (see flow chart 7.3).

4.4.5 Ensure that necessary Standard Operating Procedures (SOPs) reflecting the requirements of the GMSC are in place before GTMP/GTIMP is used.

4.4.6 Notify pharmacy as early as possible, provide associated documentation required by pharmacy and discuss to ensure compliance with Good Clinical Practice (GCP) aspects of medicines management.

4.4.7 Ensure the clinical team and other staff who may come into contact with the GTIMP or GTMP are appropriately trained in the receipt, onsite storage, onsite preparation and handling, onsite transportation, administration and disposal of GTIMP in line with GCP. This training should be documented in the site file and the individuals named on the trial delegation log.

4.5 Consultant Pharmacist for Advanced Therapy Medicinal Products and the Pharmacy Clinical Trial Lead will:

4.5.1 Work with the PI (and others where relevant) to ensure that the on-site arrangements for receiving, handling, storage and destruction of the GTIMP will be in compliance with GCP, and for non-trial use work with the relevant Clinical Director to ensure on-site arrangements for receiving, handling, storage and destruction of the GTMP will be in compliance with regulation and good practice

4.5.2 Ensure that suitable arrangements for dispensing or preparation will be in place, if applicable at site.

4.5.3 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 relevant requirements.

4.6 Non-trial use of GTMPs

For non-trial use the Clinical Director of the directorate using the medicine will be responsible for all aspects of safe delivery and disposal of the GTMP following appropriate advice/approval by the GMSC.

5. Implementation

5.1 The procedure will be disseminated through the intranet and by email from the R&D office to Principal Investigators.

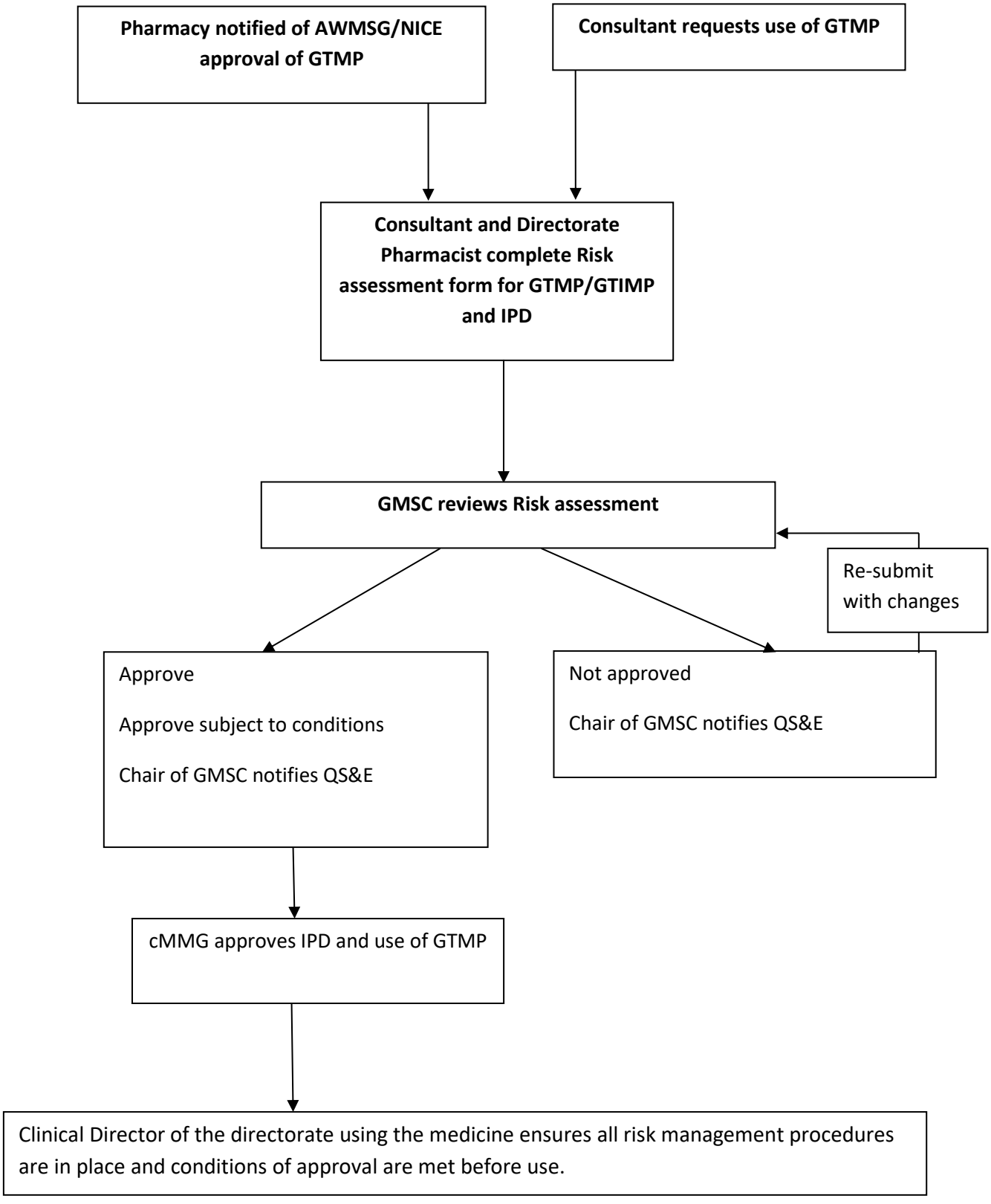
6. Review and feedback

The policy and procedure will be reviewed every three years.

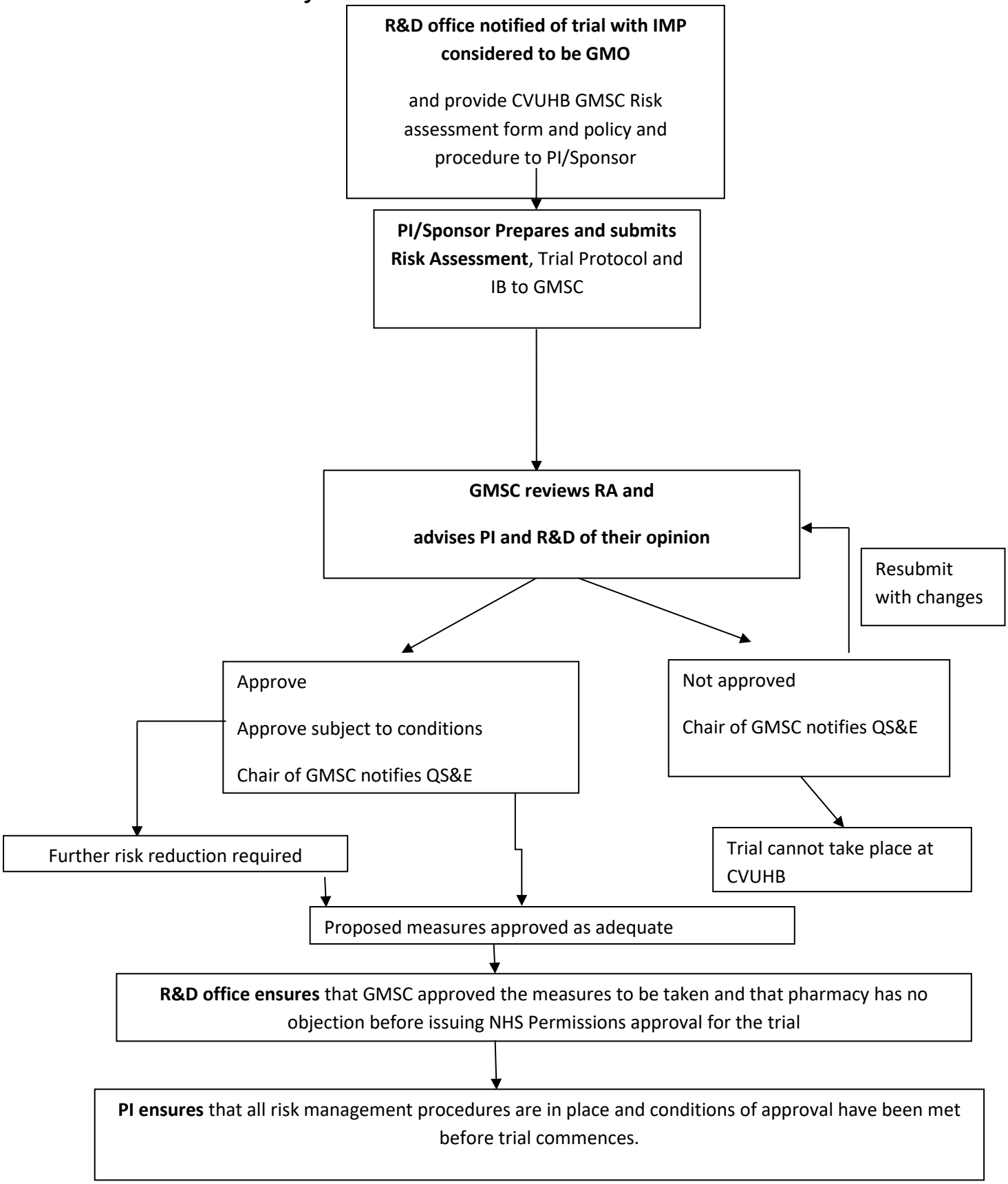
The GMSC welcomes feedback on these documents and is keen to learn from and respond to local experience. All comments should be addressed to the chair of the GMSC.

7. Flow Charts for Assessment and Approval Process

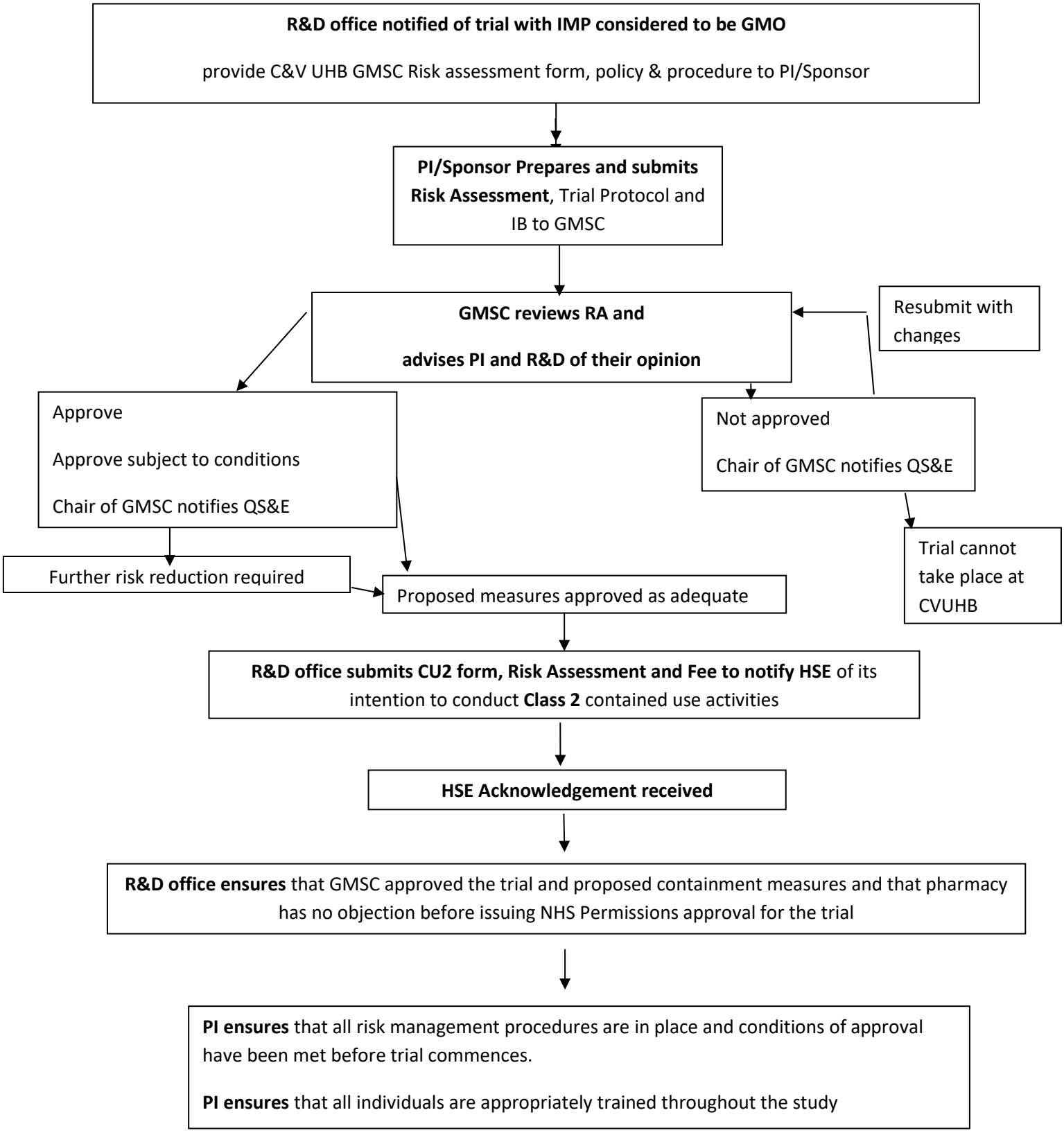
7.1 Licenced/off trial activity



7.2 Class 1 Activity



7.2 Class 2 Activity



8. GMSC Contacts

Chair: Dr Emma Kempshall (emma.kempshall@wales.nhs.uk)

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