Guidance for conducting clinical trials involving GMOs at the RMH

Purpose

The purpose of this guidance is to describe the process for sponsors and/or GMO licence holders to provide information about GMOs for use in clinical trials at RMH.

Background

Clinical trials conducted in Australia are subject to various regulatory controls to ensure the safety of participants.

The Royal Melbourne Hospital (RMH) Research Policy requires that all research in which RMH is involved complies with all applicable local, state, national and international codes of research conduct and ethical and regulatory requirements including:

- The Australian Code for the Responsible Conduct of Research, 2018 (the Code)
- National Statement on Ethical Conduct in Human Research 2007 (updated 2018)
- The Therapeutic Goods Act 1989
- Therapeutic Goods Regulations 1990
- Therapeutic Goods (Medical Devices) Regulations 2002
- Commonwealth Gene Technology Act 2000 (the Act) and Gene Technology Regulations 2001
- Victorian Gene Technology Act 2001 and Gene Technology Regulations 2011 or state regulations (other than Victoria) as applicable to multi-site studies

Dealings (activities) of Genetically Modified Organisms (GMOs) are regulated by the Gene Technology Regulator (the Regulator). The Regulator is an independent statutory office holder responsible for administering the *Gene Technology Act 2000* (the Act) and corresponding state and territory laws.

The Office of the Gene Technology Regulator (OGTR) sits within the Australian Government Department of Health and provides administrative support to the Regulator in the performance of the functions under the Act.

In administering the gene technology regulatory system, the Regulator has specific responsibility to protect the health and safety of people, and to protect the environment, by identifying risk posed by or as a result of gene technology, and by managing those risks through regulating certain dealings with GMOs.

Clinical trials involving the administration of Genetically Modified Organisms (GMOs), or GMO-modified cell products, to humans may require a licence from the Office of the Gene Technology Regulator (OGTR). Conducting clinical procedures that involve GMOs without appropriate authorisation under the Gene Technology Act 2000 (GT Act) is an offence and subject to severe penalties.

The following information may be useful:

- "How are GMOs regulated in Australia?" OGTR factsheet - an overview of the Australian regulatory system for GMOs.
- "Guidance for Clinical Trial Sponsors" OGTR guidance on requirements under the Gene Technology Act 2000 for clinical trials in humans involving GMOs.

The following tables list the timeframes and documents to be provided to the RMH site for clinical trials involving GMOs at three time points:

- at approach to site / site feasibility review
- for inclusion in ethics applications to the RMH HREC
- for inclusion in research governance (site specific authorisation) applications

Table 1: List of timeframes and information / documents to be provided to the RMH site for clinical trials involving GMOs at approach to site / site feasibility review.

Information/documentation	Purpose
The trial involves a GMO/s	To alert the site that the trial involves a GMO and additional processes/costs may be involved
Product information	Provides site staff/service departments with information necessary to assess site's ability to safely handle and administer the GMO
Licence (if Licence has been issued)	Provides site staff/service departments with information necessary to assess site's ability to comply with the conditions of the Licence i.e., storage, handling, disposal of the GMO, handling blood, urine and other samples collected from study participants RMH site is listed on the licence Note - RMH will need to have an agreement with the Licence holder outlining the responsibilities of both parties
Summary of Risk Assessment (if Licence has been issued)	Supports the site staff/service departments understanding of the risks of handling and procedures with the GMO
Classification of the GMO (if known)	i.e. Exempt Dealing, DNIR, DIR To allow site assess risk involved in conducting the dealings for the trial
Name of the Institutional Biosafety Committee (IBC) that will/has reviewed trial and RMH site processes	To confirm that an IBC will/has review/ed and confirmed the: • classification of the dealing • procedures for the dealings involved in the trial for the RMH site are appropriate • site personnel are appropriately trained
Type of GMO treatment investigational product/medicine	i.e. gene therapy, immunotherapy, vaccine etc.
Participant specific requirements	i.e. people with X condition that are also antibody negative to the vector Allows site to assess if they have the appropriate number of participants
Impact on site	Includes work practices and behaviours, where applicable, that must be followed during preparation and administration of the GMO e.g. budget implications, PPE, special handling, storage conditions, disposal procedures, handling of spills and also special handling requirements for participant samples collected for Pathology testing/processing Requirement for special storage conditions / separation of investigational product/medicine To allow site to assess if they need to organise additional items and update processes if required
Schedule of training to be provided by the Licence holder or delegate - what and when will this occur	Allows the site to identify and coordinate staff to attend training Note – scheduling should be by negotiation and well before the SIV to allow for any changes on processes to be implemented before SIV
Compliance plan information	The sponsor proposed contingency plan (if already prepared) to allow the site to assess if they site can comply with the contingency plan and/or information requested from the site so that the Licence holder can prepare/update site contingency plan.

Table 2: List of information / documents to be provided for the ethics applications of clinical trials involving GMOs.

Information/documentation	Purpose
All information from Table 1	To assist the ethical review of applications involving a GMO. List of documentation provided and any that is unavailable at the time of submission. Note: the HREC may not be able to conduct the review if documentation is missing.
Information relevant to ethical review of safety of the GMO (may be in the HREA and /or other document)	To assist in ethical review of the application Including impact on the participants for example: • If it is a once only treatment • Will the participant shed the GMO? If so, provide the duration of the shedding and information to participants describing this and associated precautions and special equipment. • Duration of follow-up. Is this life long? For gene therapy studies provide relevant information including: • Screening procedures for pre-existing immunity • The route of delivery • How the vector gets into target tissues • The duration treated cells will produce the target protein • If there will be an immune response to the vector • If there is an immune response to the vector, what treatments will this prevent in the future for the participant? Describe if there will be risks to staff and close contacts of participants including: • If there are negative health effects from GMO exposure including development of anti-GMO antibodies that may preclude future treatment opportunities?
IBC review correspondence - queries and replies	Allows HREC to understand issues raised by the IBC
Questions and answers on licence decision (if licence issued)	Plain language information to assist ethical review of trial application. This document contains a series of questions and corresponding answers on the licence application and the Regulator's decision to issue a licence for this application. Example available at https://www.ogtr.gov.au/gmo-dealings/dealings-involving-intentional-release/dir-179#documents
Summary of Risk Assessment and Risk Management Plan (if licence issued)	Plain language summary of the Risk Assessment and Risk Management Plan to assist ethical review of trial application. The documents are prepared as part of the OGTR assessment of the licence application. Brief plain language description of the licence application, the risk assessment and risk management plan.
Full **Risk Assessment and Risk Management Plan prepared by the OGTR(if licence issued)**	To assist ethical review of trial application. The document details the risk assessment and risk management plan prepared as part of the Regulator's decision-making process for this application. It explains the risk assessment context, provides an assessment of risks posed by the GMO(s) and details whether any of those risks require management. It also includes a summary of submissions received during the public consultation process.
Risk Assessment	If not prepared by the OGTR as part of a Licence review/approval.

Table 3: List of information / documents to be provided to the RMH site for Research Governance application (Site Specific Authorisation application) of clinical trials involving GMOs.

Information/documentation	Purpose
All information from Table 1	Clarify the classification of the GMO and supports appropriate review of the application
All information from Table 2	If reviewing HREC is NOT the MH HREC Provides information considered during HREC review and supports appropriate review of the application
Confirmation that the IBC has reviewed procedures and personnel for RMH site	Confirms that the procedures for the RMH site can comply with the licence conditions
Copy of certificate of GMO specific training	To allow site to demonstrate compliance with Licence conditions
List of site personnel identified to attend/that have attended the training	To allow site to demonstrate compliance with Licence conditions
GMO specific supplies	Stickers for transport boxes and equipment including fridges and freezers
Budget information	Confirmation that the sponsor will fund costs associated with additional GMO associated requirements such as PPE, gloves, syringes, labels, staff time, dedicated GMO disposal bins, space, participant supplies, etc.
Any other applicable information	

Definitions

Dealing	A procedure that involves a GMO. *The Gene Technology Act 2000* defines ***"deal with"***, in relation to a GMO, to mean the following**:** (a) conduct experiments with the GMO; (b) make, develop, produce or manufacture the GMO; (c) breed the GMO; (d) propagate the GMO; (e) use the GMO in the course of manufacture of a thing that is not the GMO; (f) grow, raise or culture the GMO; (g) import the GMO; (h) transport the GMO; (i) dispose of the GMO; and includes the possession, supply or use of the GMO for the purposes of, or in the course of, a dealing mentioned in any of paragraphs (a) to (i).
DIR	Dealing involving Intentional Release Dealings involving an Intentional Release (DIR) of GMOs into the Australian environment are dealings with GMOs which take place outside of containment facilities. These dealings must be licensed by the Gene Technology Regulator (the Regulator). Examples include experimental field trials, general/commercial releases of GM plants, GM vaccines for human or veterinary use (trial and/or general/commercial release).
DNIR	Dealing Not involving Intentional Release Dealing NOT involving an Intentional Release (DNIR) of genetically modified organisms (GMOs) into the environment are **dealings with GMOs in contained facilities** which do not meet the criteria for classification as Exempt Dealings or Notifiable Low Risk Dealings (NLRDs). Dealings with a GMO licensed as a DNIR must not involve release into the environment. These dealings must be licensed by the Gene Technology Regulator (the Regulator).
Exempt Dealing	Exempt dealings are a category of dealings with GMOs that have been assessed over time as posing a very low risk (i.e. contained research involving very well understood organisms and processes for creating and studying GMOs). The only legislative requirement for exempt dealings is that they must not involve an intentional release of a GMO into the environment. Exempt dealings are described in Schedule 2 of the *Gene Technology Regulations 2001* (the Regulations).
GMO	Genetically Modified Organism
IBC	Institutional Biosafety Committee
Licence	Approval mechanism for dealings involving release of a GMO into the environment (DIR or DNIR)
OGTR	Office of the Gene Technology Regulator (Australian Regulator for GMOs)