



Australian Government

Department of Health and Aged Care
Office of the Gene Technology Regulator

December 2024

Risk Assessment and Risk Management Plan (consultation version)

for

DIR 210 – Clinical trials of controlled infection with seasonal Influenza viruses

Applicant – Doherty Clinical Trials Ltd

This RARMP is open for consultation until 7 February 2025.

Written comments on the risks to human health and safety and the environment posed by this proposed clinical trial are invited. You may make your submission

via mail to: The Office of the Gene Technology Regulator, MDP 54 GPO Box 9848,
Canberra ACT 2601 or

via email to: ogtr@health.gov.au.

Please note that issues regarding food safety and labelling, and marketing and trade implications do **not** fall within the scope of these evaluations as they are the responsibilities of other agencies and authorities.

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Summary of the Risk Assessment and Risk Management Plan (Consultation Version)

for

Licence Application No. DIR 210

Introduction

Influenza is an acute respiratory viral infection caused by influenza A or B viruses, with up to 650,000 deaths worldwide annually. For most healthy adults, seasonal influenza is a self-limited illness from which complete recovery is expected. Understanding the physiological and immunological responses of humans to these viruses is critical to develop vaccines and antiviral drugs for the control of influenza.

Doherty Clinical Trials Ltd (DCT) is seeking approval to use genetically modified (GM) influenza viruses similar to naturally circulating influenza viruses to better understand influenza infection and test the efficacy of potential vaccines and therapeutic drugs. The GM influenza viruses are made using gene technology and are considered GMOs.

Healthy volunteers will receive a safe dose of the GM influenza viruses within a clinical facility in combination with or without a potential vaccine or therapeutic drug.

The study will be conducted under strict ethical guidelines and safety protocols in an approved clinical trial facility, considering OGTR and good clinical practice guidelines. In addition, the applicant has proposed control strategies to restrict the spread and persistence of the GMO(s) in the environment.

Clinical trials in Australia are conducted in accordance with requirements of the *Therapeutic Goods Act 1989*, which is administered by the Therapeutic Goods Administration (TGA). Therefore, in addition to approval by the Regulator, DCT would also require authorisation from TGA before the trial commences. Clinical trials conducted in Australia must also be conducted in accordance with the [National Statement on Ethical Conduct in Human Research](#) and with the [Guidelines for Good Clinical Practice](#) of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. DCT would also require approval from the Department of Agriculture, Fisheries and Forestry for import of the GMOs.

The Regulator has produced a Risk Assessment and Risk Management Plan (RARMP) for this application. The assessment concludes that the proposed clinical trial poses negligible to moderate risks to human health and safety. Draft licence conditions for the trial have also been prepared. The Regulator is inviting submissions regarding the RARMP and the draft licence conditions to help inform the decision on whether to issue a licence.

The application

Project Title	Clinical trials of controlled infection with seasonal Influenza viruses
Parent organism	Seasonal Human Influenza Virus A and B (including H1N1 and H3N2)
Principal purpose	The initial aim is to evaluate the safety and infectivity of recombinant seasonal human influenza viruses in healthy volunteers. These GM viruses will then be used to assess the effectiveness of therapeutic drugs or vaccine candidates to prevent and control influenza infection.
Genetic modifications	Recombinant influenza virus A and B produced using gene technology (reverse genetics) similar to naturally circulating strains of wild-type seasonal influenza
Previous clinical trials	One completed challenge study in the United States (NCT04978454) One ongoing challenge study in the United States (NCT06476275)
Proposed limits and controls	
Proposed duration	5 years
Proposed trial size	Up to 150 clinical trial participants
Proposed locations	Clinical Trial Ward located in East Melbourne.
Proposed controls	Trial participants will be isolated in secure rooms Staff will be trained and experienced in preventing spread of infection Staff will wear personal protective equipment (PPE) while conducting dealings with GMO including GMO administration, serving food, patient care, checks and monitoring as required Trial participants will remain isolated for 7 days post administration Waste potentially contaminated with GMOs will be disposed of in GMO-labelled bin and collected by external service providers

Risk assessment

The risk assessment process considers how the genetic modifications and proposed activities conducted with the GMO might lead to harm to people or the environment. Risks are characterised in relation to both the seriousness and likelihood of harm, taking into account information in the application (including proposed controls), relevant previous approvals and current scientific/technical knowledge. Both the short- and long-term impact are considered.

Credible pathways to potential harm that were considered included exposure of people or animals to the GMOs and whether there is the potential for reassortment with other viruses. Potential harms that were considered in relation to these pathways included ill health and increased disease in people or animals.

The RARMP determined that the proposed clinical trial presents **negligible to moderate risks** to the health and safety of individuals. Licence conditions have been implemented to mitigate the risks associated with this clinical trial.

Important factors in reaching the conclusions of the risk assessment included:

- the GMOs would not be more pathogenic than circulation strain of influenza

- the trial participants will remain isolated for the duration of the contagious period
- extensive PPE would be worn by staff conducting dealings.

Risk management plan

The risk management plan describes measures to protect the health and safety of people and to protect the environment by controlling or mitigating risk. The risk management plan is given effect through licence conditions.

The RARMP determined that the proposed clinical trial presents **negligible to moderate risks** to the health and safety of individuals. Licence conditions have been implemented to mitigate the risks associated with this clinical trial. In addition, since this is a clinical trial, the licence includes limits on the number of trial participants, the facility used, exclusion criteria, and as well as a range of controls to minimise the potential for exposure of people other than trial participants to the GMO. There are also several general conditions relating to ongoing licence holder suitability, auditing and monitoring, and reporting requirements, including an obligation to report any unintended effects.

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Abbreviations

Act	<i>Gene Technology Act 2000</i>
AEs	Adverse Events
AIVC	Australian Influenza Vaccine Committee
°C	Degrees Celsius
CDC	Centers for Disease Control and Prevention
cGCP	current Good Clinical Practice
cGMP	Current Good Manufacturing Practice
CHIM	Controlled Human Infection Model
CRO	Clinical Research Organisation
Cth	Commonwealth of Australia
CTN	Clinical Trial Notification
CTX	Clinical Trial Exemption
DAWE	Department of Agriculture, Water and the Environment
DIR	Dealings involving Intentional Release
DNA	Deoxyribonucleic Acid
EU	European Union
Eudra CT	European Union Drug Regulating Authorities Clinical Trials
dpi	days post administration
FSANZ	Food Standards Australia New Zealand
GM	Genetically Modified
GMO	Genetically Modified Organism
HA	haemagglutinin
HGT	horizontal gene transfer
HREC	Human Research Ethics Committee
(H1N1) pdm09	2009 pandemic influenza strain
IAV	Influenza A virus
IBV	Influenza B virus
IATA	International Air Transport Association
IBC	Institutional Biosafety Committee
ICH-GCP	<i>Guidelines for Good Clinical Practice</i> of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
M2	Matrix 2 protein
M2SR	M2 deficient Single Replication vaccine
NA	neuraminidase
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NIH	National Institutes of Health
NHMRC	National Health and Medical Research Council
NLRD	Notifiable Low Risk Dealings
NPAAC	National Pathology Accreditation Advisory Council

OGTR	Office of the Gene Technology Regulator
PCR	Polymerase Chain Reaction
PPE	Personal Protective Equipment
QC	Quality Control
QLD	Queensland
RARMP	Risk Assessment and Risk Management Plan
Regulations	Gene Technology Regulations 2001
Regulator	Gene Technology Regulator
RNA	Ribonucleic Acid
RG	Reverse Genetics
SAEs	Serious Adverse Events
TCID ₅₀	Tissue Culture Infectious Dose 50%
TGA	Therapeutic Goods Administration
TSD	<i>The Regulator's Guidelines for Transport, Storage and Disposal</i>
WHO	World Health Organisation
WHO CCRI	WHO Collaborating Centre for Reference and Research on Influenza

Chapter 1 Risk assessment context

Section 1 Background

1. An application has been made under the *Gene Technology Act 2000* (the Act) for Dealings involving the Intentional Release (DIR) of genetically modified organisms (GMOs) into the Australian environment.
2. The Act and the Gene Technology Regulations 2001 (the Regulations), together with corresponding State and Territory legislation, comprise Australia's national regulatory system for gene technology. Its objective is to protect the health and safety of people, and to protect the environment, by identifying risks posed by or as a result of gene technology, and by managing those risks through regulating certain dealings with GMOs.
3. Section 50 of the Act requires that the Gene Technology Regulator (the Regulator) must prepare a Risk Assessment and Risk Management Plan (RARMP) in response to an application for release of GMOs into the Australian environment. Sections 50, 50A and 51 of the Act and sections 9 and 10 of the Regulations outline the matters which the Regulator must take into account and who must be consulted when preparing the RARMP.
4. The Risk Analysis Framework (OGTR, 2013) explains the Regulator's approach to the preparation of RARMPs in accordance with the Act and the Regulations. The Regulator has also developed operational policies and guidelines that are relevant to DIR licences. These documents are available from the Office of the Gene Technology Regulator (OGTR) website).
5. Figure 1 shows the information that is considered, within the regulatory framework above, in establishing the risk assessment context. This information is specific for each application. Potential risks to the health and safety of people or the environment posed by the proposed clinical trial are assessed within this context. Chapter 1 provides the specific information for establishing the risk assessment context for this application.

RISK ASSESSMENT CONTEXT	
The GMO Modified genes Novel traits	Proposed GMO dealings Activities Limits Controls
Parent organism (comparator) Origin and taxonomy Cultivation and use Biology	Previous releases Australian approvals International approvals
Receiving environment Environmental conditions: abiotic and biotic factors Production practices Related organisms Similar genes and proteins	

Figure 1. Summary of parameters used to establish the risk assessment context, within the legislative requirements, operational policies and guidelines of the OGTR and the RAF

6. In accordance with Section 50A of the Act, this application is considered to be a limited and controlled release application, as the Regulator was satisfied that it meets the criteria prescribed by

the Act. Therefore, the Regulator was not required to consult with prescribed experts, agencies and authorities before preparation of the RARMP.

1.1 Interface with other regulatory schemes

7. Gene technology legislation operates in conjunction with other regulatory schemes in Australia. The GMOs and any proposed dealings conducted under a licence issued by the Regulator may also be subject to regulation by other Australian government agencies that regulate GMOs or GM products, including Food Standards Australia New Zealand, the Australian Pesticides and Veterinary Medicines Authority, the Therapeutic Goods Administration (TGA), the Australian Industrial Chemicals Introduction Scheme and the Department of Agriculture, Fisheries and Forestry (DAFF).

8. The DAFF regulates products imported into Australia to protect Australia from biosecurity risks. Under the Biosecurity Act 2015, the importation of biological material such as live GM treatments require a permit from the DAFF.

9. Medicines and other therapeutic goods for use in Australia are required to be assessed for quality, safety and efficacy under the Therapeutic Goods Act 1989 and must be included in the Australian Register of Therapeutic Goods. The TGA is responsible for administering the provisions of this legislation. Clinical trials of therapeutic products that are experimental and under development, prior to a full evaluation and assessment, are also regulated by the TGA through the Clinical Trial Approval scheme or the Clinical Trial Notification scheme.

10. Approval by a Human Research Ethics Committee (HREC) is also a fundamental requirement of a clinical trial. HREC review is a part of the research governance process carried out by an institution that is responsible for the quality, safety and ethical acceptability of research carried out under their auspices. HRECs review research proposals involving human participants to ensure that they are ethically acceptable and meet relevant standards and guidelines. Elements of research to be considered include research merit and integrity, justice, beneficence, and participant consent.

11. The National Health and Medical Research Council (NHMRC) has issued the National Statement on Ethical Conduct in Human Research, 2018 (National Statement) (National Health and Medical Research Council et al., 2018) which is the principal ethics guideline setting out the requirements for the ethical design, review and conduct of human research in Australia. The Therapeutic Goods Act 1989 requires an HREC to review and monitor all clinical trials of unregistered therapeutic goods. The HREC must be registered with the NHMRC and constituted and operating in accordance with the National Statement.

12. In terms of risk to individuals participating in a clinical trial, the TGA (as the primary regulatory agency of investigational products), the trial sponsor, the investigators and the HREC responsible for each trial site all have roles in ensuring participant's safety under the Therapeutic Goods Act 1989 and the requirements of the National Statement. However, where the trial involves a GMO, authorisation is also required under gene technology legislation. To avoid duplication of regulatory oversight, and as risks to trial participants are addressed through the above mechanisms, the Regulator's focus is on assessing risks posed to people other than those participating in the clinical trial, and to the environment. This includes risks to people preparing and administering the GMO, and risks associated with import, transport and disposal of the GMO.

13. The clinical facility is a medical facility. These type of facilities are regulated by State and Territory governments and adhere to professional standards for safety (NSQHS), disease control (Australian Guidelines for the Prevention and Control of Infection in Healthcare (2019) and handling of pathology samples (NPAAC).

Section 2 The proposed dealings

14. Doherty Clinical Trials (DCT) is seeking approval to use genetically modified (GM) influenza viruses similar to naturally circulating seasonal influenza viruses to better understand influenza infection and test the efficacy of potential vaccines and therapeutic drugs. The GM influenza viruses are made using gene technology and are considered GMOs. Healthy volunteers will receive a safe dose of the GMO within a clinical facility with or without a potential vaccine or therapeutic drug. This licence covers dealings occurring at the DCT site and disposal of waste generated during each trial. All other dealings including import, transport to and from the DCT site and sample analysis will be covered by a notifiable low risk dealings (NLRD) authorisation held by WHO Collaborating Centre for Reference and Research on Influenza (WHO CCRI).

15. The dealings involved in the proposed clinical trials are:

- Conduct the following experiments with the GMOs:
 - Preparation of the GMOs for administration
 - Administer the GMO to clinical trial participants, one dose in each nostril by nasal spray
 - Collection of samples from trial participants
- Transport the GMOs for disposal
- Dispose of the GMOs

and the possession (including storage), supply and use the GMO for the purposes of, or in the course of, any of these dealings.

2.1 The proposed limits of the trial (duration, scale, location, people)

16. The trials would take place at a DCT clinical trial facility located in Melbourne over a five-year period from the date of issue of the licence. The applicant intends to administer GMOs to up to 150 trial participants.

17. DCT will conduct the studies with groups of 6 to 12 participants at a time to reduce the exposure of staff and the environment to GMOs.

18. Inclusion and exclusion criteria are in place to limit the impact, transmission, and exposure of GMOs to non-participants. The details can be found in section 2.4.3.

19. Participants will only be infected once with a virus on day 0.

20. Only seasonal influenza virus A and B viruses will be included. Highly pathogenic flu strains such as H5 or H7 sub-types are not proposed.

2.2 The proposed controls to restrict the spread and persistence of the GMOs in the environment

21. The applicant has proposed a number of controls to minimise exposure to the GMO, and to restrict the spread and persistence of the GMOs in the environment. These include:

- Participants will be accommodated separately in secure isolation rooms within the clinical facility during the clinical trial for at least 7 days.

- During the administration process, precautions will be taken due to minimise the exposure of staff to aerosols. Staff will wear PPE, including a N95 facemask, and the participant will wear a surgical mask for 1.5 hours post-administration and anytime staff members access the room during the post-care period.
- The administration procedure will be sharp-free to avoid inadvertent administration to study staff.
- Appropriate spill kits and disinfectants for surface and hand decontamination will be provided within each isolation room.
- All staff will be required to be vaccinated with the most current and available seasonal influenza vaccine.
- All waste potentially contaminated with GMOs will be collected by external service providers and destroyed via incineration.

2.3 DCT clinical trial facility

22. The clinical trial will be conducted in the DCT clinical ward area within the DCT clinical trial facility over a period of five years. The DCT clinical ward is staffed with qualified personnel and equipped with appropriate infrastructures to conduct this clinical trial safely.

23. DCT has established a facility dedicated to supporting early-phase infectious disease clinical studies, including controlled human infection model (CHIM) studies. The DCT facility features a purpose-built clinical ward area with six secure isolation rooms to accommodate participants during the clinical trial. All study activities during this period, including participant monitoring and sample collection, will be conducted within these secure isolation rooms.

24. Rooms are on the second floor of the building, only accessible by authorised and trained staff using a security swipe card. The DCT clinical ward area and corridors around the isolation rooms are monitored by CCTV cameras.

25. Each room is under negative pressure in relation to the hallway, with an individual ventilation system where no exhaust air is vented or recirculated into another room, or into the corridors. Each room has its own exhaust to the outside. Doors are properly sealed to prevent the entry and exit of insects and vermin. Each room's door can be securely locked and is self-closing. All windows are non-openable and fully sealed.

26. The applicant has stated that:

- Each isolation room has its own ensuite bathroom for the sole use of each participant and a handwash facility.
- Each room contains a handsfree GMO waste bin.
- Appropriate decontamination wipes are provided in and outside each room, next to the door to wipe down the door handles and high touchpoints near the door each time a staff member leaves the room.
- Adequate supply of clean gloves and masks will be available in each room for participants and separately for the staff member that enters the room.

- Appropriate spill kits and disinfectants will be present in each room to inactivate any spills immediately.
- Adequate hand washing or hand sanitising facilities are in the participants bedrooms, and outside the door of their rooms.

2.4 Details of the proposed activities

2.4.1 *Manufacture of the GMO*

27. The GMO will be supplied by the USA National Institutes of Health (NIH) and imported to the WHO CCRRI laboratory at the Doherty Institute using their Biosecurity Import Permits. The virus will be imported, handled, stored, disposed of, and transported under their NLRDs.

28. The applicant has provided details about the first GMO proposed to be used under this licence. Test results confirmed the genetic sequence of the GM virus is similar to wild-type virus. However, a single nucleotide difference was observed in the genome sequence compared to the wild-type virus, which corresponds to the nucleoprotein (NP) gene segment.

2.4.2 *Conduct of the clinical trials*

29. The proposed clinical trial, initially conducted, is an open-label in-patient trial of sero-susceptible healthy participants (antibody titre of $\leq 1:20$). The aim of the initial trial is to evaluate the safety, infectivity, clinical response, viral shedding and immune response following nasal administration of the GM recombinant influenza virus.

30. The participant will be admitted to the facility two days prior to receiving the GMO.

31. Day 0: The patient will receive a single 1 mL dose intranasally with a volume of 0.5 mL per nostril.

32. Day 1-7: study nasal swabs will be collected each day from day 1 to 7 after administration for detection of influenza virus. Blood samples will be collected on days 1, 2, 4, 5 and 6. Air sample collection will occur in the participant's room over a 30-minute period on days 2, 4 and 6. Stool and urine samples will be collected on days 1, 4 and 7.

33. If the participant is still shedding virus at day 6, they will be given an antiviral treatment. The participant can be discharged on day 7 if they are PCR negative on day 7. If the participants are still PCR positive on day 7, they will be retained in the unit until day 8 post challenge when they will be discharged regardless of PCR result.

34. DCT has proposed that all clinical trials will follow the same established protocol described above. The GMOs used will include H3N2 and the H1N1 influenza variant synthesised using a reverse genetics method. However, it is important to note that highly pathogenic influenza strains, including H5 and H7 sub-types, will not be included in these studies.

35. Aside from investigating influenza infections using the GMOs (influenza A and B), the applicant proposes to conduct challenge studies using non-GMOs. The primary objective of these challenge studies is to assess and evaluate the effectiveness of various drug candidates and vaccines against these influenza strains. Trial participants may receive an influenza vaccine followed a few days later by the intranasal administration of a GMO influenza strain to determine the efficacy of a novel vaccine. Similarly, antiviral drugs would be administered following infection with a GM influenza strain to assess their efficacy for the treatment of influenza infection.

2.4.3 Selection of trial participants and behavioural requirements

36. In the proposed clinical trial, the GM influenza viruses would be administered intranasally to healthy volunteers. To be enrolled in the trial, participants must meet the following relevant inclusion and exclusion criteria:

Inclusion criteria

- General good health, without significant medical conditions that would interfere with subject safety, as defined by medical history, physical examination, screening laboratory tests, and ECG at a screening evaluation.
- Trial participant must be willing to adhere to the requirements of the study and willing to communicate with the Investigator and understand the requirements of the study.
- Women of childbearing potential (WOCBP) are required to practice a highly effective form of contraception during the course of the study.

Exclusion criteria

- History of clinically significant or currently active neurologic, cardiac, respiratory, hepatic, rheumatologic, autoimmune, or renal disease.
- Trial participants with household contacts who are at higher risk for influenza-related complications including persons ≥ 65 years of age or < 5 years of age, and pregnant individuals.

2.4.4 Import and storage of the GMO

37. The import, supply and storage of the GMOs prior being moved to the trial site would be covered by an NLRD and not under this licence.

2.4.5 Personal protective clothing (PPE)

38. The applicant advised that appropriate PPE (fitted N95 mask, gown, goggles, gloves, closed shoes and shoe coverings), suitable to protect a staff member from exposure to the GMOs, will be worn when working with the GMOs. Clinical trial staff conducting dealings with the GMOs including administration of the GMO to trial participants and clean-up of potential spills would wear PPE. Staff collecting waste and serving food would also wear the same PPE while the trial participant is still shedding the GMOs. All the staff and external service providers (waste disposal and laundry) will also follow donning and doffing procedures.

PPE DONNING PROCEDURE

- Before entering the room, the staff member will sanitise their hands and put on a gown, closed shoes, shoe covering, and goggles. They will sanitise their hands again, put on a pair of gloves, and can then enter the participants' rooms.

PPE DOFFING PROCEDURE

- Before exiting the isolation room, staff must ensure the trial participant is more than 1m away with their mask on. The staff member will then remove the gown, shoe coverings and gloves to be disposed in the GMO-labelled bin in the room, sanitise their hands, wipe down

their safety glasses and door handle with separate antiviral wipes (70%+ alcohol or Clinel wipes or similar).

- On exiting the room, the staff member must ensure the door is closed and locked. Re-sanitise their hands again, remove their face mask to dispose of in the GMO waste bin outside of the room and re-sanitise their hands again.

2.4.6 *Intranasal administration of the GMO*

39. The GMO would be transported in a sealed, unbreakable, leak-proof screw cap vial to the point-of-administration to the trial participant within the isolation room. The outer container would be labelled to indicate that it contains a GMO, the OGTR licence number and contact details of an appropriate clinical trial staff member.

40. A disposable bench cloth will be laid down on a table previously wiped with a disinfectant. The transport container will be placed on this table and opened. The vial with the GMO will be removed and inspected to ensure it is intact. The GMO will be removed using a syringe, but no needle would be used. The patient will receive a single dose of 1 mL (approximately 1×10^6 50% tissue culture infectious dose (TCID₅₀) intranasally using the MAD Nasal™ Intranasal Mucosal Atomisation (Figure 2) in a volume of 0.5 mL per nostril.

41. Participants will receive the GMO via a nasal spray while lying on their backs, wearing goggles, an apron or gown, and a surgical mask. They will remove the mask during the administration and then place the mask back on. To administer the GMO, the nasal sprayer is inserted into the subject's nostrils and a fine spray is expelled into the nasal cavity. The nasal sprayer distributes the GMO almost exclusively to the upper and lower airway of the trial participant.



Figure 2: MAD Nasal™ Intranasal mucosal atomisation device

42. The staff will remain in the room for 30 minutes for further observation of the trial participant. After 10 minutes, the trial participant can remove their goggles, and at the 30-minute mark, they will be allowed to remove their gloves and apron, thoroughly sanitise their hands, put on a new surgical mask. They will be required to wear the surgical mask for 1 more hour.

43. After the GMO administration, the DCT staff will change their gloves after disposing of the used ones and putting on fresh gloves. Once the staff have completed the procedure, the bench cloth will be disposed of in the GMO-labelled waste bin. The table, surfaces, transport containers, and any non-disposable equipment will be cleaned with the appropriate disinfectant provided in the room. Any tissues or paper towels used during this process will also be disposed of in the GMO waste bin located in the room.

44. The DCT staff will exit the room following PPE doffing procedure.

2.4.7 Sample collection and analysis

45. Samples collected from trial participants may be analysed in Australia. The transport and analysis of the samples will be done under DCT and WHO CCIR NLRDs.

46. The proposed clinical trial will involve the collection of five types of samples from the volunteers: nasal swab, exhaled air, blood, urine, and stool. The collection of these samples is covered under this licence. All the samples will be collected by trained DCT personnel wearing appropriate PPE as described in section 2.4.5

47. Nasal swabs will be collected each day from day 1 to 7 after administration for detection of influenza virus. The samples will be tested for the presence of viral RNA by reverse transcriptase-polymerase chain reaction (RT-PCR).

48. Blood samples will be collected on days 1, 2, 4, 5 and 6 using a needle and syringe or vacutainer. The blood will be collected from the participant's vein into sealed collection tubes.

49. Air sample collection will take place in the participant's room over a 30-minute period on days 2, 4 and 6 using an air sampling device. The device will be cleaned and removed from the room, and the air samples will be extracted and tested for the presence of aerosolised GMOs.

50. Stool and urine samples will be collected on days 1, 4, and 7. A staff member wearing PPE as described in section 2.4.5 will collect the samples from a bedpan. The remaining stool and urine will be flushed into the toilet in the participant's room.

2.4.8 Transport and disposal of the GMO

51. Samples collected from the volunteers will be transported, stored and analysed under the WHO CCIRI's NLRD. The only transport covered under this licence would be the transport within the DCT facility and transport of potentially contaminated waste or bedding from the DCT facility.

52. All disposable materials used during the administration procedure or for the collection of samples from participants and any other contaminated waste (e.g. sprayers, gloves, needles, tissues) would be disposed of according to infectious medical waste management procedures. The outer container of the waste would be labelled to indicate that it contains GMOs. External service waste contractors would transport and dispose of all GMO waste, which would be destroyed by high-temperature incineration.

53. Waste contractors would be selected based on their experience and capability in disposing of infectious clinical waste and laundering/disposing of linen which has been contaminated with infectious substances. Waste contractors would handle GMO contaminated waste using the same safety precautions for handling infectious waste.

54. All mattresses, bedding, and linen will undergo decontamination and washing by an approved commercial laundry vendor specialising in infection control in hospitals, 48 hours after the participant has left the unit.

2.4.9 Training of clinical trial personnel

55. DCT would be responsible for ensuring training of personnel and compliance with OGTR licence conditions.

56. All clinical trial staff would be trained in Good Clinical Practice (GCP) requirements.

57. Persons handling the GMO during administration (i.e. the Principal Investigator, the Study Coordinator and medical staff assisting in administration of the GMO to participants), would be trained in all procedures specific to the GMO including handling, spill procedures, containment and disposal. Records of this training would be kept within the clinical trial master file. A copy of the licence would also be kept in the clinical trial file at the site.

58. Before each trial begins at DCT, a full practice run will be conducted and observed with all staff involved. Any outstanding issues detected will be documented, resolved and signed off before the trial begins. After each trial, a “lessons learnt” forum will be conducted, documented and actioned.

2.4.10 Contingency plans

59. In case of unintentional release of the GMO due to an accidental spill, the spill would be reported to DCT by clinical trial staff trained in the OGTR reporting requirements. The local IBC would also be notified of loss of containment or suspected loss of containment. Appropriate spill kits and disinfectants will be present in each room to inactivate any spills. DCT staff will clean spills using appropriate kits and disinfectants according to AS/NZS 2243.3:2022 Appendix F while wearing appropriate PPE.

60. In the event of a spill, the spill management plan includes:

- Containing the GMO(s) to prevent further dispersal.
- Ensuring cleanup personnel wear PPE.
- Decontaminating the affected area with an effective chemical disinfectant (e.g 80%v/v Ethanol, 1% F10SC).
- Decontaminating cleanup materials and protective clothing.
- Notifying the licence holder promptly after the spill.
- The licence holder will inform the Regulator as soon as possible.

61. In case of exposure of people to the GMO: If DCT staff show signs of a respiratory infection, they will be required to isolate, a nasal swab will be taken to test for a virus using RT-PCR. If influenza is found, its genetic sequence will be compared with that of the GMO to confirm its identity. If the strain of influenza is identified as the GMO, the staff member will be treated with antivirals.

2.4.11 Accountability and Monitoring

62. Every primary container of the GM investigational product would be accounted for, in line with standard clinical practice.

63. Severe Adverse Events (SAEs) occurring at any time during the study would be recorded. Reported Adverse Events (AEs) would also be recorded for each participant following administration of the GMO. A Safety Monitoring Committee would be available to review available safety data at specified time points and as needed.

Section 3 Parent organism – Influenza virus

64. The parent organism is the human Influenza A and B. In this case, the study virus will be generated from viral RNA isolated from wild-type virus (wt) using reverse genetics. The GM viruses

will be a copy of wt without any intended genetic modification. The characteristics of the non-GM parent organism (Influenza A and B) provide a baseline for comparing the potential for harm from dealings with GMOs. As such, the relevant biological properties of influenza virus will be discussed here.

3.1 Understanding Influenza: a general perspective

65. Influenza A is much more common (typically 75% of total influenza cases) than Influenza B. Both Influenza A and B can cause outbreaks and epidemics but only Influenza A can cause pandemics. Influenza A can move from animals, including birds, to people, while Influenza B develops only in humans. Influenza A viruses are classified into subtypes based on surface proteins. Currently circulating in humans are A(H1N1) and A(H3N2) influenza viruses. Influenza B viruses are not classified into subtypes but can be broken down into lineages, either B/Yamagata or B/Victoria lineage.

66. Human influenza A and B viruses are highly infectious viruses that cause human influenza (flu), a contagious disease of the respiratory system. Flu viruses generally transmit through large aerosol droplets that are generated when an infected person coughs, sneezes or talks. They are also transmitted when contaminated surfaces, such as hands or tissues, make contact with the mucous membranes.

67. The onset of flu is sudden, and it is accompanied by malaise, persistent runny nose, cough, headache, sore throat and high fever. Infection normally resolves in less than two weeks without the need for treatment in healthy individuals. Symptoms may be reduced if antiviral drugs are administered within 48 hours of initial symptoms (Stiver, 2003). Fatalities can occur when individuals who are weakened by influenza develop pneumonia and bronchitis from a secondary bacterial or viral infection.

68. Those at highest risk of the more severe symptoms include the elderly, young children, pregnant women and the immunocompromised. Influenza generally aggravates respiratory conditions such as asthma.

69. Influenza infection during pregnancy can result in the spread of the virus into the aorta, causing a peripheral "vascular storm" marked by increased inflammatory mediators in mice models. This vascular storm is linked to high rates of morbidity and mortality during pregnancy, as well as the subsequent perinatal complications associated with influenza infection (Liong et al., 2020).

70. Seasonal influenza spreads easily in crowded areas like schools and nursing homes. In temperate climates, it mainly happens in winter, while in tropical regions, it can occur throughout the year, causing irregular outbreaks (Ali et al., 2022; Pica and Bouvier, 2012). The incubation period is typically about 2 days but can range from 1–4 days (Uyeki et al., 2022).

71. Approximately one billion cases of influenza are reported annually, including 3–5 million cases of severe illness and 290,000 to 650,000 respiratory deaths each year. The annual attack rate or proportion of people who become ill after exposure is estimated at 5%–10% in adults and 20%–30% in children (WHO, 2018). Influenza viruses are endemic in Australia (Health, 2015). Ninety percent of deaths in children under 5 years of age are due to influenza-related lower respiratory tract infections in developing countries (WHO, 2023).

72. In 2023, Australia reported 252,296 confirmed influenza cases and 376 influenza-associated deaths to the National Notifiable Disease Surveillance System. During the same period, there were 3,696 sentinel hospital admissions, with 256 (7%) directly admitted to the ICU. Children aged 5-9

years had the highest influenza notification rates, followed by children aged 0-4 years (NNDSS, 2023).

73. In Australia, Aboriginal and Torres Strait Islander peoples experience a significantly higher incidence of influenza, leading to severe health consequences within these communities. The flu is a prominent factor contributing to hospitalisations among Indigenous Australians. Factors such as limited access to healthcare services, underlying health conditions, and social determinants of health play a crucial role in this increased vulnerability (Weinman et al., 2020).

74. Shedding of detectable amounts of influenza virus from the respiratory tract generally begins one day after infection, with symptoms appearing two days after infection. Viral replication peaks approximately two days after infection and declines slowly from there. Shedding typically continues for a further three to five days and can last up to nine days in healthy adults. Shedding does not significantly differ between influenza types or subtypes. Shedding in young children lasts for a longer time period and generally lasts for up to seven days (Carrat et al., 2008; Suess et al., 2010; WHO Writing Group, 2006).

75. Recovery of viable influenza viruses from stool samples has rarely been reported, indicating that the respiratory tract may be the primary source of shedding, as the levels of viral RNA detected from nasal swabs was much higher than the levels detected in stools (Minodier et al., 2019).

76. Influenza viruses are rarely detected in blood using PCR methods, however when it is detected, it is generally observed in severely ill patients, who required hospitalisation (Stramer et al., 2012; Suess et al., 2012; Tse et al., 2011).

77. The biology of Influenza A and B viruses has been described in detail in the RARMPs for DIR-137 and DIR-144 (clinical trials with GM Influenza viruses).

3.2 Genome and virion structure of influenza A virus

78. The genome of influenza A viruses is made up of eight single-stranded, negative-sense RNA segments as shown in Table 1.

Table 1. Segments of influenza A virus

Segment number	Segment code	Largest protein encoded by segment
1	PB2	polymerase basic 2
2	PB1	polymerase basic 1
3	PA	polymerase acidic
4	HA	haemagglutinin
5	NP	nucleoprotein
6	NA	neuraminidase
7	M	matrix
8	NS1	non-structural protein

79. The RNA segments do not exist as naked RNA but are always associated with multiple copies of viral nucleoprotein (NP) that protect it from host ribonucleases. Each genomic segment exists as a ribonucleoprotein (RNP) with the viral RNA wrapped around the outside of the nucleoprotein (NP) oligomer and attached to the polymerase complex (Figure 3).

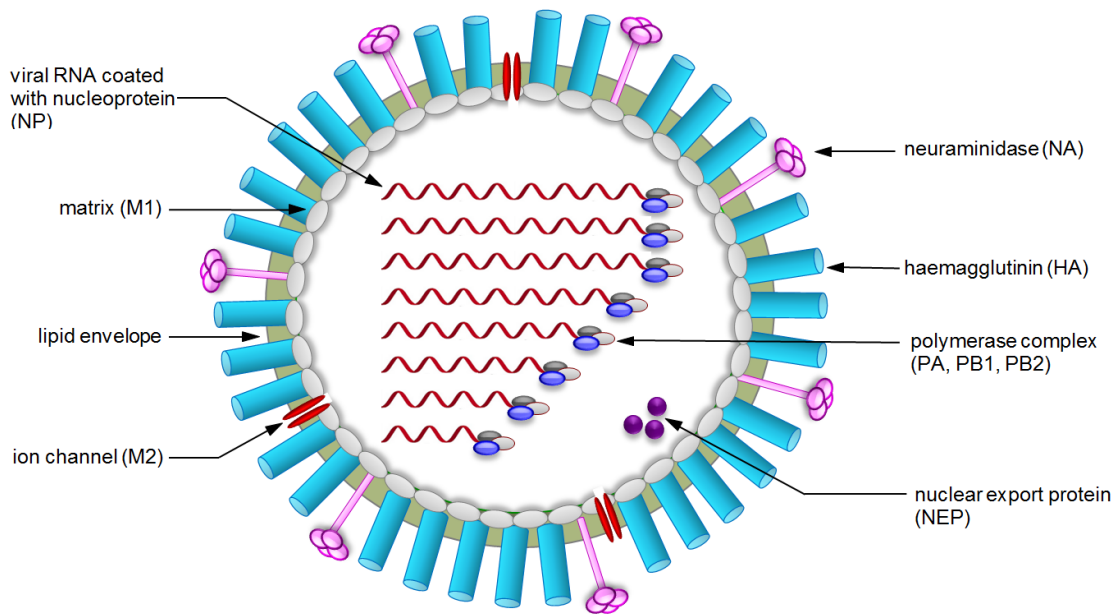


Figure 3. Schematic representation of the influenza virus particle

80. The eight RNPs are enclosed in a layer of matrix protein (M1). M1 is the most abundant protein in the virus; it drives virus budding and controls the intracellular trafficking of RNPs. The viral envelope, which is a lipid bilayer derived from the host cell membrane with viral proteins inserted, lies just outside the M1 layer.

81. The lipid envelope has three integral membrane proteins, namely haemagglutinin, neuraminidase and proton-selective ion channel (M2). Haemagglutinin and neuraminidase are the major antigenic determinants on the surface of the influenza virus. The M2 proton channels are essential for uncoating and budding of viral particles.

82. Influenza B virus is physiologically similar to Influenza A virus and looks similar under an electron microscope. Influenza B consists of eight negative-strand RNA segments, which encode 11 proteins. Of these, nine are also found in influenza A virus: three RNA-dependent RNA polymerase subunits (PB1, PB2, and PA), haemagglutinin (HA), nucleoprotein (NP), neuraminidase (NA), matrix protein (M1), and two non-structural proteins (NS1 and NS2). Two proteins, NB and BM2, are unique to influenza B virus. NB is thought to function as an ion channel protein; however, studies have concluded otherwise. In addition, NB protein is also not necessary for viral replication (Hatta and Kawaoka, 2003). BM2 is essential for producing infectious viruses; the BM2 knockout virus, lacking BM2, do not grow substantially (Imai et al., 2004).

3.3 Haemagglutinin (HA) and Neuraminidase (NA): role in cellular entry of influenza viruses

83. Haemagglutinin has two main functions: receptor binding and facilitating fusion of viral and host membranes. This transmembrane protein is the most abundant protein on the virion surface. Human influenza A viruses have one of three types of haemagglutinin, H1, H2, or H3.

84. The major target cells for human influenza viruses are epithelial cells lining the respiratory tract. The exposed surfaces of these cells are glycosylated and the glycans have sialic acid which is the receptor for influenza viruses.

85. Newly budded viruses are not infectious as their intact haemagglutinin (HA0) must first be activated by proteolytic cleavage conducted by sialic acid into two peptides (HA1 and HA2). Cleavage generates a short hydrophobic sequence at the N-terminus of HA2 called the fusion peptide and this peptide is required to initiate fusion of viral and host membranes. HA1 forms the receptor binding site for the host sialic acid receptors. HA1 and HA2 remain intertwined after cleavage. Since receptor binding and infection cannot proceed in the absence of the fusion peptide, the pathogenicity of any viral subtype is determined, in part, by the ease of HA0 cleavage.

86. After receptor binding, influenza viruses enter the host cell either by receptor mediated endocytosis or macropinocytosis, depending on their morphology (Rossman et al., 2012). These entry mechanisms are triggered when a virus attaches to the cell surface. The internalised virus is encapsulated in an endosome and at this point, the viral RNPs are separated from the host cytoplasm by the endosomal membrane, the viral envelope and the capsid (Figure 4).

87. Release into the cytoplasm requires the fusion of the viral and host (endosomal) membranes but membrane fusion is an energetically unfavourable process. Mediation of membrane fusion is the second function of haemagglutinin. The host cell acidifies the contents of the endosome to enable destruction by acid hydrolases. The drop in pH triggers a conformational change in haemagglutinin. This exposes the previously buried fusion peptide, which then inserts into the endosomal membrane, resulting in haemagglutinin being attached to both membranes. Several haemagglutinin trimers, acting in concert, distort the membranes and pores form, allowing membrane fusion of the host endosome membrane and the viral envelope.

88. Neuraminidase hydrolyses the glycosidic bond between sialic acid (N-acetyl neuraminic acid) and galactose. Without neuraminidase, large aggregates of viruses form at the surface of the infected cell, due to binding between haemagglutinin on the newly budded viral particles and sialic acid on the cell surface, as well as between haemagglutinin and sialic acid on adjacent particles. Aggregation of viral particles is the main reason flu viruses do not spread as quickly in the absence of neuraminidase (Palese et al., 1974; Liu et al., 1995). Two neuraminidase subtypes are found in human influenza A viruses (Sempere Borau and Stertz, 2021).

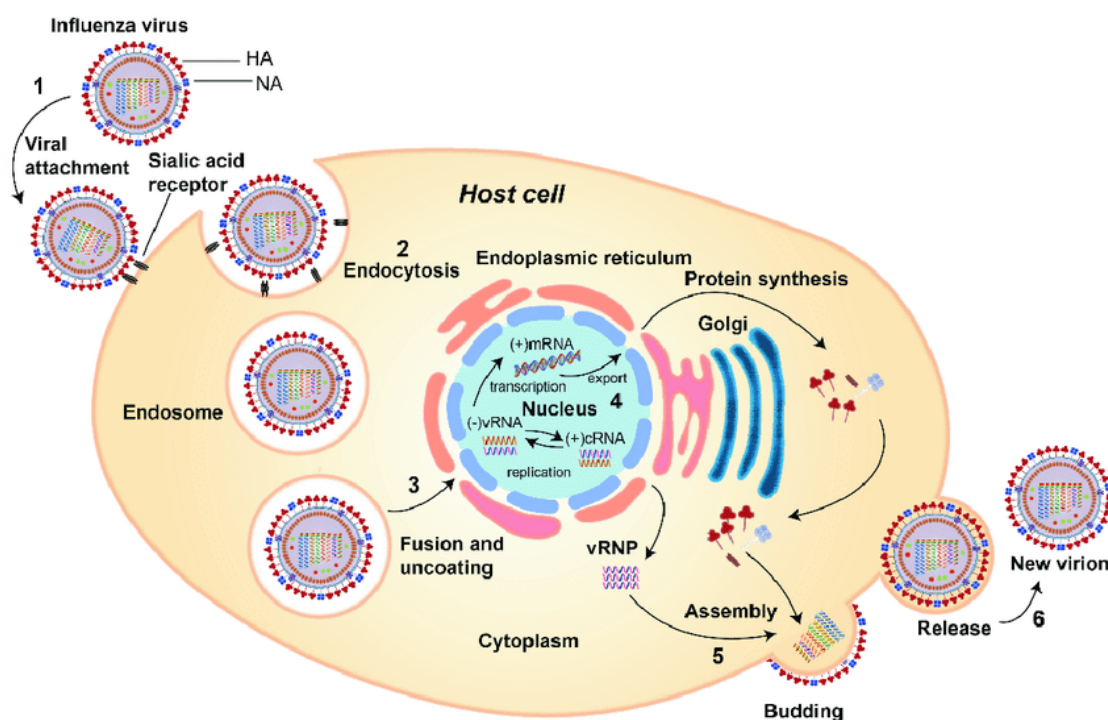


Figure 4: The life cycle of influenza virus: (1) virus attachment to sialic acid receptor via HA; (2) entry of the virus into the host cell via endocytosis; (3) fusion and uncoating of virus particle; (4) vRNPs entry into the nucleus followed by transcription and replication of the viral RNA genome and then export of vRNPs from the nucleus; (5) assembly of viral components and budding at the host cell membrane; (6) new virion release from the host cell.

89. The respiratory epithelium, which is the target tissue of influenza viruses, is protected by a layer of mucus up to 50 µm thick. The main protein in mucus is mucin, a highly glycosylated protein with sialic acids decoys that mimic the true receptors on epithelial cells. Influenza viruses that bind these 'decoy' receptors are trapped in the mucus and removed during mucus clearing, which is part of the innate defence system. Neuraminidase frees the viruses from binding of the decoy receptor, thereby enabling them to penetrate the protective mucus layer during infection.

90. Neuraminidase also increases virulence of flu viruses by compromising the immune defences at the mucosal surface. It removes sialic acid from T-cells in the mucosa and from immunoglobulin A (IgA)-producing B cells, adversely affecting their function. It also de-sialidates IgA, resulting in it being cleared more quickly by the hepatic system (Bhatia and Kast, 2007).

91. Recent efforts have significantly advanced our understanding of how the influenza A virus (IAV) enters host cells. Studies have shown that two subtypes of bat-derived influenza A virus (H17N10 and H18N11) found in South and Central American bats do not rely on sialic acid to enter cells. Additionally, there has been increased focus on the role of the NA protein in viral entry. It is crucial to balance the functional properties of the HA and NA proteins to effectively penetrate the sialylated mucus layer, attach to and enter epithelial cells, and facilitate the spread of virions (Wagner et al., 2002; Hu et al., 2017; Sempere Borau and Stertz, 2021; Dou, 2017).

3.4 The haemagglutinin-neuraminidase balance

92. The levels of haemagglutinin and neuraminidase activity have to be very finely balanced for productive viral infection. Haemagglutinin and neuraminidase both bind sialic acid but have opposing functions: haemagglutinin binds the receptor for cellular entry while neuraminidase cleaves the receptor to free the virus. If the level of neuraminidase activity is too high, the receptor will be cleaved before the virus can undergo endocytosis and the host cell will not be infected. Conversely, if the level of neuraminidase activity is too low, the receptor will be cleaved too slowly during budding, and viral progeny will aggregate and be prevented from infecting other cells. Some haemagglutinin-neuraminidase combinations recur while others are rarely observed in both natural and laboratory-derived reassortants. The replication fitness of these reassortants could be explained by a mismatch in receptor binding and release (Wagner et al., 2002).

93. The presence of a functional match between the hemagglutinin and neuraminidase is a clear indicator of the pandemic potential of zoonotic viruses. An investigation on swine progenitors and human viruses from the 2009 pandemic reveals that a functional balance of HA binding and NA cleavage is found in human viruses, but not in the swine progenitors. Therefore, a functional match between the hemagglutinin and neuraminidase is necessary for efficient transmission between species (Xu et al., 2012).

3.5 Viral replication

94. Viral replication does not involve a DNA intermediate. The negative sense genomic RNA (vRNA) serves as the template for the synthesis of both mRNA and the complementary genomic strand of RNA (cRNA). cRNA is the full-length transcript of vRNA while mRNA is a truncated transcript. Transcription and replication of the influenza virus occur in the nucleus.

95. Influenza viruses replicate very quickly. Host cells start shedding new progeny viruses from around 6 hours after infection (WHO, 2015).

96. Up to 90% of virus-infected cells fail to release infectious progeny. Analysis of viral progeny shows that propagation-competent virions containing one each of the eight RNPs are outnumbered by semi-infectious virions with an incomplete set of RNPs (Brooke et al., 2014). The propagation-competent fraction of virions varies widely between different strains of influenza virus.

3.6 Mutation and reassortment

97. Point mutations in the main antigenic determinants, haemagglutinin and neuraminidase, result in antigenically novel viruses that can cause disease in previously resistant or immune hosts. This effect is called antigenic drift.

98. Point mutation rates are very high in single stranded RNA viruses, estimated at two to three errors per replicated genome (Drake, 1993; Pauly et al., 2017; Sanjuan et al., 2010).

99. When a cell is co-infected, or ‘Superinfected’ with two influenza viruses of the same type (i.e. two influenza A viruses or two influenza B viruses), each of the eight vRNPs in the progeny virus can originate from either infecting virus because the genome is segmented. Such viral progeny is called reassortants.

100. There are many factors that influence the frequency of novel reassortant viruses. Reassortment is dependent on the occurrence of co-infection of Influenza A viruses (IAV). The frequency of co-infection is dependent upon the viral dose received, with higher doses resulting in increased co-infection rates in vitro and in vivo (Bodewes et al., 2012; Marshall et al., 2013). In addition, viral spread of the first infection prior to administration with the second infection can increase the probability of co-infection and reassortment. Both co-infection and reassortment rates were reduced in cell culture when the first infection occurred in conditions that did not allow for viral spread (Marshall et al., 2013).

101. Another factor affecting the rate of co-infection is the time delay between the primary and secondary infections. Co-infection is strongly inhibited in a time-dependent manner, with inhibition starting to take effect by 2, 6 or 12 hours post infection in vitro (Dou et al., 2017; Huang et al., 2008; Marshall et al., 2013; Sun and Brooke, 2018). The range in inhibition start times found in the literature may be due to experimental differences, such as dose used. When guinea pigs were intranasally inoculated with two IAVs with a time delay of 12 hours between infections, nearly half of the virus isolates were found to be reassortants. However, when the time delay was increased to 24 hours between infections, none of the virus isolates were reassortants (Marshall et al., 2013). These data suggest that there is a small temporal window where co-infection with two different IAVs can occur.

102. Multiple factors can promote or prevent the establishment and spread of reassortant viruses. Generally, more frequent reassortment is thought to take place between IAV strains that are more genetically similar, and the more divergent they are, the less likely reassortants are to establish and spread (Brooke, 2017; Marshall et al., 2013; Phipps et al., 2017; Villa and Lassig, 2017). There may also be genetic incompatibilities between parental strains that result in attenuated progeny, with reduced fitness, such as incompatibilities between the three polymerase segments (Phipps et al., 2017) or an HA/NA imbalance. Consequently, differences between parental strains can limit reassortment or heavily bias the production of reassortants with specific gene segment combinations.

103. Studies on the occurrence of reassortants in humans have suggested that there is both negative selection against reassortants, and restriction in the gene segment combinations being produced, reducing the effective rate of reassortment to much lower levels than has been reported in animals (Sobel Leonard et al., 2017; Villa and Lassig, 2017). This was suggested to be in part due to lower doses of IAVs received by the humans compared to animals and the fact that humans have a much larger respiratory tract surface area than guinea pigs or ferrets, which may result in lower co-infection rates (Sobel Leonard et al., 2017).

104. A cell could be co-infected with influenza A viruses from two different host organisms e.g. a human influenza virus and a swine influenza virus. These two influenza A viruses could reassort, resulting in a novel combination of the antigenic determinants HA and NA. The creation of novel antigenic combinations is known as antigenic shift. While the majority of possible reassortants would be expected to be non-viable and have reduced fitness compared to the parental strains, some novel combinations could potentially lead to the emergence of new influenza strains.

3.7 Host range

105. Influenza viruses are generally host specific. The principal reservoir of human influenza A viruses are humans, but new human subtypes can arise from avian reservoirs.

106. Direct bird to human transmission is not common and it has not resulted in a sustainable pathogen as avian subtypes transmit poorly between humans. To cross the species barrier, the avian virus must acquire changes in the receptor specificity of haemagglutinin and neuraminidase and replicate efficiently at the lower human body temperature. Avian influenza virus replication is somewhat restricted by the 32°C ambient temperature of the human nose. The temperature of the avian gut, where the receptors are present and replication would occur, is estimated at 41°C.

107. Human infections with avian influenza viruses generally occur via domesticated intermediates. These infections have not resulted in sustained human to human transmission. The greatest risk occurs during the handling and slaughtering of live infected poultry. Proposed routes of infection include the inhalation of infectious aerosols or aerosolised faeces and contact with contaminated surfaces.

108. Companion animals such as dogs and cats can be susceptible to human influenza. A human-like H3N2 influenza virus has been isolated from dogs. These dogs shed the virus, had fever, sneezed and coughed (Chen et al., 2015). Cats can be infected with H3N2 canine influenza (Song et al., 2015). Infected cats shed the virus, had elevated temperatures and severe pulmonary lesions.

109. Outbreaks of influenza occur sporadically among farmed animals including swine and mink (Gagnon et al., 2009). Influenza viruses are able to be transmitted from swine to humans, if there is close contact (e.g. pig farmers). Subsequent person-to-person transmission is very limited (Olsen et al., 2002). The viruses may also transmit from humans to swine (Shin et al., 2006).

110. Avian influenza viruses are not endemic in Australia and are not expected to become endemic in the long term, as Australia is not on the migratory flight path of water birds (ducks, geese and swans) that act as a reservoir for the disease (OCVO, 2010). However, there is currently an outbreak in Victoria, New South Wales and ACT (Health, 2024).

111. Swine influenza viruses have been detected in Australian pig populations, with isolated cases of human infection with swine-origin influenza viruses reported in people who work on pig farms, and one case of an adolescent acquiring swine influenza after attending an agricultural fair in September 2018 (Animal Health Australia, 2018; Deng et al., 2020; Smith et al., 2019).

112. In Australia, the outbreak of equine influenza in 2007 and of avian influenza (H7N2) in 2013 did not result in human infections. Horses have a sialic acid receptor that is similar to that of avian species (Suzuki et al., 2000).

113. In May 2024, an H7N3 HPAI strain was detected at a poultry farm near Meredith, in the Golden Plains Shire, Victoria. Six other poultry farms in the shire are now infected, with the most recent confirmed on 24 June (Victoria, 2024).

3.8 Environmental stability and decontamination methods for influenza virus

114. Influenza viruses remain viable on non-porous surfaces such as stainless steel and plastic for up to 24 hours, and on semi porous surfaces such as cloth, paper and tissues for eight to twelve hours (Bean et al., 1982a).

115. Influenza viruses can be effectively inactivated using many commonly used disinfectants and heat treatment. Washing hands with soap and water can prevent contact transmission of the virus, as this disrupts the viral lipid envelope. Surfaces can be chemically decontaminated with standard disinfectants such as bleach, 70% ethanol, 2% alkaline glutaraldehyde and 5 to 8% formalin. Physical decontamination includes moist heat at 121°C for 20 minutes or dry heat at 70°C for 5 minutes, 80°C for 2.5 minutes or 90°C for 1 minute (Jeong et al., 2010; Pathogen Regulation Directorate, 2011a, b).

3.9 Antiviral treatments for influenza virus

116. Antiviral agents are 70-90% effective as short-term prophylactics (Monto, 2003). Neuraminidase inhibitors such as oseltamivir (Tamiflu) and zanamivir (Relenza) may shorten the period of influenza infection.

117. Baloxavir is an antiviral medication for treatment of influenza A and influenza B. It was approved for medical use both in Japan and in the United States in 2018 and is taken as a single dose by mouth. Baloxavir acts on the cap-dependent endonuclease (CEN), an influenza virus-specific enzyme in the polymerase acidic (PA) subunit of the viral RNA polymerase complex and thereby inhibits the transcription of influenza virus genomes resulting in inhibition of influenza virus replication.

118. M2 inhibitors such as amantadine and rimantadine, block the M2 ion channel and in doing so, prevent uncoating of the virus and progression of the infection. The spread of a single mutation in the M2 protein has resulted in widespread resistance to this class of drugs.

119. Antivirals like Oseltamivir and Baloxavir have been shown to be effective in preventing the transmission of influenza. A trial conducted by Roche found that a daily dose of 75 mg of Oseltamivir reduces viral spread, as measured by nasal shedding of influenza viruses (Cowling, 2024). The median time to cessation of viral shedding post one dose of (Baloxavir) Xofluza® is 24 hours (95% CI: 24.0, 48.0) (Roche, 2024). Additionally, Baloxavir has been reported to be more effective than Oseltamivir, as it reduces viral load within 24 hours of administration at a daily dose of 80 mg (Umemura et al., 2020).

3.10 Flu vaccines

120. Annual vaccination against circulating flu strains is strongly recommended for high-risk groups such as the elderly and the immunocompromised (Centers for Disease Control and Prevention, 2008). The Australian Immunisation Handbook recommends annual influenza vaccination for everyone 6 months of age and over (Australian Technical Advisory Group on Immunisation (ATAGI), 2018).

121. The most common flu vaccines are inactivated (killed) vaccines, which can be divided into whole virus vaccines, split virus vaccines and subunit vaccines. In whole virus vaccines, an immune response is elicited by intramuscular injection of the intact but killed virus. Split virus vaccines use whole virus that has been disrupted by a detergent. By comparison, subunit vaccines only use partially purified haemagglutinin and neuraminidase protein. Inactivated vaccines do not offer effective protection against influenza viruses that have shifted antigenically from the recommended target strains or promote cellular immunity. Unlike inactivated vaccines, live attenuated flu vaccines are able to provide broad cross-protection against antigenically divergent influenza strains.

122. The influenza vaccine virus strain is updated every year to provide coverage and protection for the circulating virus strains. Due to the combination of high mutation rates and antigenic selection driving mutations in haemagglutinin and neuraminidase, circulating virus strains are always changing. Consequently, the WHO recommends flu strains for targeting with vaccines (targeted strains) twice annually. Recommendations are made in February for the Northern Hemisphere flu season and in September for the Southern Hemisphere flu season. The WHO's recommendations are evaluated by the Australian Influenza Vaccine Committee (AIVC) which provides advice to the TGA on the composition of the seasonal flu vaccine to be supplied each year in Australia.

3.11 Risk group of influenza virus

123. The Australian Standard 2243.3:2022 Safety in Laboratories Part 3: Microbiological safety and containment (Standards Australia/New Zealand, 2022) classifies influenza as a Risk Group 2 organism. Highly pathogenic strains of Influenza are classified as Risk group 3 organisms, although these are not proposed under this DIR.

Section 4 The GMOs – nature and effect of genetic modifications

124. The applicant has provided information about the initial GMOs to be used under this licence (RG-A/Texas/71/2017 (H3N2) and H1N1). It is expected that subsequent GMOs will be produced in a similar fashion and have the same characteristics.

125. The manufacturing process of the wild-type influenza virus is intended to produce similar copies of the original virus without any genetic modifications. This means that the genetic composition of the replicated virus remains similar, preserving the characteristics of the wild-type virus, although point mutations could occur during the generation of these GMOs.

4.1 The production of GMOs

4.1.1 Parental stain: The Influenza A and B

126. The first parent organism is H3N2, which is a strain of the human influenza A virus. This specific strain has been utilised in various studies and clinical trials to understand the host response to influenza and to develop improved vaccines and treatments. A challenge study conducted by the NIH was completed in 2022 without reporting any serious effects. However, an increase in the frequency and severity of systemic and respiratory symptoms was observed at increasing dose levels. The most commonly reported symptoms were fever, severe headache, malaise, stuffy nose, sore throat, and sneezing (NIAID, 2023).

127. In April 2009, a new virus emerged in Mexico and California, leading to the first pandemic of the 21st century. This virus, labelled A/(H1N1) pdm09, spreads rapidly from person to person and is not related to any circulating inter-pandemic viruses. It is a quadruple reassortant virus, comprising two swine-origin viruses, one avian-origin virus, and one human-origin virus. Molecular studies have identified the presence of North American H3N2 triple reassortant viruses circulating among swine, a

classic swine H1N1 virus, and an "avian-like" swine H1N1 virus circulating in Europe and Asia. This "new" virus has proved to be remarkably different from the classic seasonal influenza H1N1 viruses and the viruses used to prepare vaccines. The GMO is derived from the pandemic strain but is now considered a seasonal strain (Al Farroukh et al., 2022; Baldo et al., 2016).

128. Other influenza A and B seasonal viruses may be used under this licence.

4.1.2 Production of recombinant influenza virus

129. An eight-plasmid DNA transfection system is typically used for the rescue of infectious influenza A and B virus from cloned cDNA. In this plasmid-based expression system, viral cDNA is inserted between the RNA polymerase I (pol I) promoter and terminator sequences. The eight plasmids contain cDNA encoding 10 proteins and able to be transcribed into negative vRNA. This entire pol I transcription unit is flanked by an RNA polymerase II (pol II) promoter and a polyadenylation site. The orientation of the two transcription units allows the synthesis of negative-sense viral RNA and positive-sense mRNA from one viral cDNA template. This pol I–pol II system starts with the initiation of transcription of the two cellular RNA polymerase enzymes from their own promoters, presumably in different compartments of the nucleus. The interaction of all molecules derived from the cellular and viral transcription and translation machinery results in the generation of infectious influenza A virus (Hoffmann et al., 2000) (Figure 5).

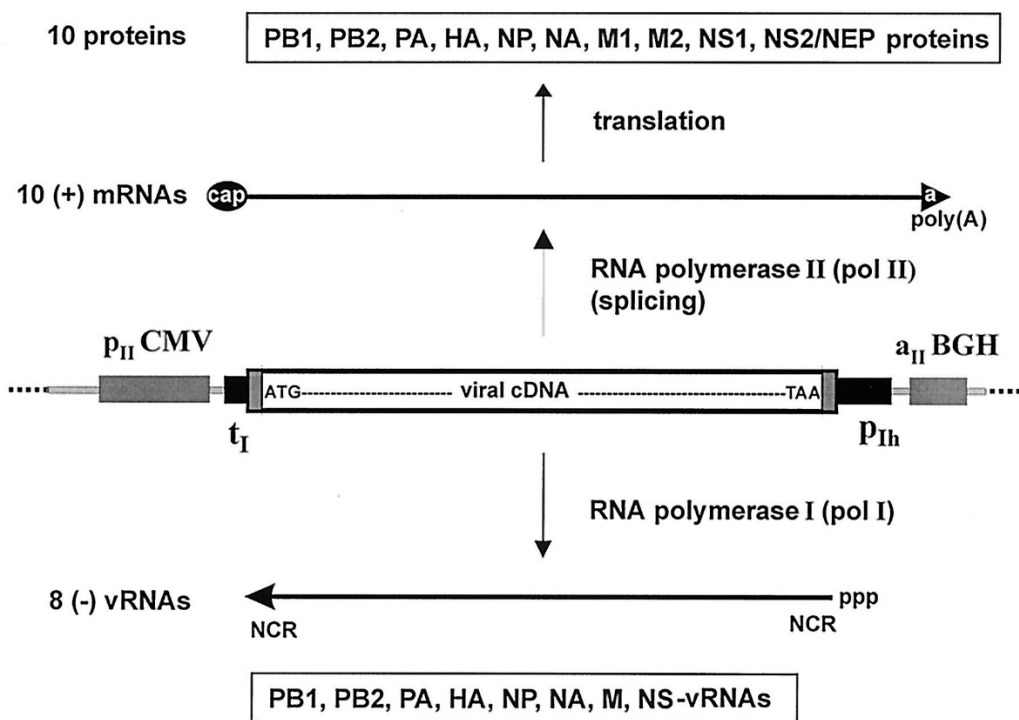


Figure 5: Schematic representation of the pol I–pol II transcription system for synthesis of vRNA and mRNA.

130. The process of generating the virus involves four steps. Firstly, the viral RNA is isolated from the wild-type virus. Next, the viral RNA is used to produce cDNA using a RT-PCR. To ensure that the viral cDNAs derived from RT-PCR amplification in the expression plasmids do not have unwanted mutations, the inserted cDNAs are sequenced. Finally, a suitable cell is used to transfect the cDNA and produce the targeted virus. Finally, the virus is propagated in HEK293 suspension (Hoffmann et al., 2002). (Figure 6).

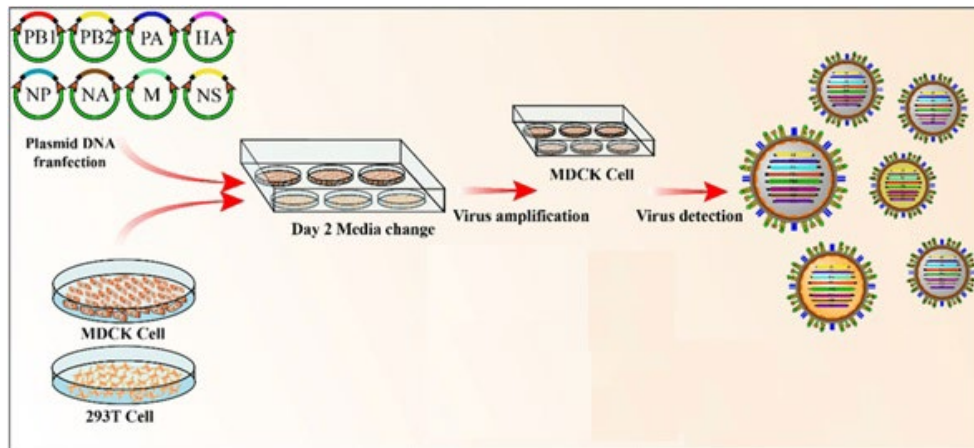


Figure 6: Schematic diagram of the influenza virus 8-plasmid reverse genetic operation process.

131. The reverse genetic system described earlier is also used to generate influenza B virus (Hoffmann et al., 2002; Jackson et al., 2002).

4.2 Characterisation of the GMOs

132. The characteristics of the GMOs have been assessed based on data obtained from experiments using the proposed GMO viruses generated using similar techniques. These viruses have alternative HA and NA segments derived from different strains of Influenza A and B viruses.

4.2.1 Viral replication of the GMOs *in vitro* and *in vivo*

133. The GMOs (RG- influenza virus-A and B), like wild-type Influenza strains, are able to replicate in human epithelial cells from the human respiratory tract, and respiratory tracts of animal models of influenza (mice, hamsters, and ferrets).

4.2.2 Genetic stability of the GMOs

134. The replication process of the wild-type influenza virus involves the generation of exact copies of the original virus without any genetic modifications. This means that the genetic composition of the replicated virus remains unchanged, preserving the characteristics of the wild-type virus. However, a single nucleotide difference was observed in the genome sequence of the RG-A/Texas/71/2017 compared to the consensus WT sequence in the nucleoprotein (NP) gene segment. The applicant has stated that any subsequent GMOs produced will be tested to confirm that are not more pathogenic than the initial circulating strain of influenza.

135. The ribonucleoprotein (RNP) complex structure is the functional unit upon which the replication and transcription of influenza viruses depend. In this complex, NP not only stabilises the structure but also regulates viral RNA transcription and replication by interacting with the viral polymerase. Additionally, NP is known to interact with various host factors to facilitate viral replication, evade immunity, and regulate apoptosis (Hung et al., 2020).

136. Several studies were conducted to investigate the effect of NP mutation on influenza A replication, virulence, and inter-species transmission. Mutations in the NP protein affect the viral polymerase. However, a mutation in NP alone cannot change the pathogenicity of the influenza A virus, as this pathogenicity depends on the HA and NA surface proteins (Danzy et al., 2014; Hu et al., 2017; Hung et al., 2020).

137. Studies have reported that the RG-influenza virus, produced using this method, does not show any significant genetic differences from the wild-type influenza virus (Hoffmann et al., 2002; Jackson et al., 2002; Lekcharoensuk et al., 2012).

138. Xiao et al. conducted a human challenge study to investigate single nucleotide polymorphisms (SNPs) and assess the intra-host evolution of the Influenza A virus. In this study, healthy volunteers were intentionally infected with the influenza strain A/California/04/2009 (H1N1). Nasal wash samples were collected, and genetic sequencing was performed. Additionally, virus samples were gathered from a small number of naturally infected patients from 2009 and sequenced for comparison. The genetic sequences from the challenge study were compared to a reference sequence, which was derived from the inoculant virus used for the study, as well as to those from naturally infected individuals. The researchers discovered that the inoculant virus evolved rapidly, with new SNPs emerging and some previous SNPs disappearing. This rapid evolution was attributed to interactions with individual hosts. Furthermore, the study identified differences between the inoculant and natural viruses, suggesting that changes occurred during cell culture and passage. Overall, the findings highlight the swift and spontaneous evolution of the influenza virus, emphasising the need for continuous monitoring and research. (Xiao et al., 2019a). While single point mutations can occur during the manufacture of these GMOs, significant changes to the pathogenicity of the GM influenzas compared to the parent organism seem unlikely. Influenza viruses are known to evolve rapidly, and any novel trait are more likely to be the result of natural evolution rather than being directly related to their production.

4.2.3 Nonclinical studies

139. In vivo, characterisation of RG-A/Texas/71/2017 (H3N2) compared with the seasonal influenza virus from which it was derived was conducted in mice, hamsters, and ferrets. In mice, infection with either the wild-type (wt) or GMO led to similar outcomes. Mice did not show any change in weight or infection profile, post-infection with either virus.

140. Hamsters did not display any clinical signs of infection. However, virus replication and pathology in respiratory tissues clearly distinguished infected animals from healthy animals. Both viruses induced clear pathological effects in the lungs at day 3 post-infection, which were completely resolved by day 14 post-infection.

141. In ferrets, both wt and the GMO caused similar mild diseases, resulting in minimal (5%) weight loss from which the ferrets recovered. Viral replication caused moderate pathological effects in the lungs, which were clearly distinguished from those of healthy animals.

142. Al Farroukh et al. (2022) conducted a study to examine the pathogenicity and toxicity of 21 A(H1N1) pdm09 (2009 pandemic strain) influenza viruses, including A/Arkansas/08/2020 H1N1, using a mouse model. In the toxicity studies, ten mice were given a high dose of fresh, undiluted virus administered to the nasal fossae. It was found that 50% of the H1N1 virus strains were highly toxic, with A/Arkansas/08/2020 causing 80% mortality in the mice. They proposed this high mortality rate was attributed to the high dose of the virus administered to the mice (Al Farroukh et al., 2022).

143. Memoli et al. investigated and compared the effects of the wt and RG-A/CA/04/2009/H1N1 virus on mice and ferrets. The amount of viral RNA in the mice lungs was quantified on day 5 and day 14 post-administration. The results showed no significant difference between the amount of recombinant and the wild-type viruses on either day 5 or day 14 and no difference in weight loss between the ferrets (Memoli et al., 2015).

144. These pre-clinical studies show that the effect of the wt virus or the equivalent virus produced by reverse genetics (GMO) are the same. Symptoms are dose-dependent and can be more significant in immunosuppressed animals.

4.2.4 Clinical studies

145. No clinical studies have been conducted with the proposed GMOs in Australia. However, six studies were approved in the USA. Two of the clinical trials utilised the GMO (A/Texas/71/2017 H3N2), which will also be used in this clinical trial. The first study aimed to determine a safe dose for the challenge virus. The second study focused on identifying volatile markers in exhaled breath and expression markers in saliva for the early detection of infection following pathogen exposure. Further information is provided in Chapter 1, Section 6.

146. In medical research, human challenge studies involve intentionally infecting healthy participants to study disease progression or test experimental treatments. One famous example is Edward Jenner's use of cowpox in 1796 to create the first vaccine, leading to the eventual eradication of smallpox (Riedel, 2005).

147. Influenza human challenge studies are summarised in Table 3.

Table 3. Influenzas Challenge studies

Title of the study	Year	Influenza Virus used in the study	Conclusion
Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: randomised controlled trials for prevention and treatment (Sherman et al., 2019).	1999	A/Texas/36/91 (H1N1)	Healthy participants (N = 117) were infected with influenza A/Texas/36/91 (H1N1), the results concluded severity of the symptoms can be reduced with prophylaxis and early treatment with oseltamivir.
Efficacy and tolerability of the oral neuraminidase inhibitor peramivir in experimental human influenza: randomised, controlled trials for prophylaxis and treatment (Barroso et al., 2005)	2005	A/Texas/36/ 91/H1N1 and B/ B/Yamagata/16/88	Healthy participants (N = 288) were infected with influenza A/Texas/36/ 91/H1N1 and B/ B/Yamagata/16/88. The results showed that an oral dose of 200 mg twice daily or 400 mg once a day was effective for influenza A, and that prophylaxis with peramivir did not significantly reduce viral shedding. The number of participants was 288.
Deep sequencing of 2009 influenza A/H1N1 virus isolated from volunteer human	2019	RG- A/California/04/2009(H1N1)	These volunteers (N=15) were infected with a RG-influenza A/California/04/2009(H1N1) and wt virus. The virus was then deep-sequenced and

challenge study participants and natural infections (Xiao et al., 2019a; Xiao et al., 2019b)			compared with the wild-type virus to understand single nucleotide polymorphism (SNP). Many SNP sites in challenge patients and naturally infected patients were found, many not identified previously. The SNPs identified and phylogenetic analyses, showed that intra-host evolution of the virus is different in challenge participants and naturally infected patients.
A Dose-finding Study of a Wild-type Influenza A(H3N2) Virus in a Healthy Volunteer Human Challenge Model (Han et al., 2019)	2019	RG-A/Bethesda/MM1/H3N2	Healthy participants (N = 49) were infected with influenza RG-A/Bethesda/MM1/H3N2 to investigate the safe dose of the challenge virus. They concluded the model is safe and can induce mild to moderate influenza disease (MMID).

148. In 2015, Memoli et al. conducted a challenge study involving 46 healthy participants. They were given a virus (RG-A/CA/04/2009) to determine the dose needed to cause mild to moderate influenza infection. The participants received a dose of 107 TCID₅₀ intranasally using a nasal atomizer. Nearly 70% of the participants showed both viral shedding and symptoms, and the model closely mimicked natural infection. Importantly, none of the participants experienced any adverse effects (AE) (Memoli et al., 2015).

149. Carrat et al. reviewed 56 different influenza challenge studies and concluded that infection from a challenge stock induced only mild disease. They found that one third of participants had a fever, and one fifth of participants developed lower respiratory symptoms. All symptoms were only observed transiently, and no medical intervention was required (Carrat et al., 2008b; Memoli et al., 2016).

150. The National Institute of Allergy and Infectious Diseases (NIAID) conducted an influenza challenge study with 60 patients. In this study, 4 cohorts of patients received varying doses of RG-A/Texas/71/2017 (H3N2). The study did not report any serious adverse effects (SAEs) from day 1 to day 29. However, some mild effects were observed, including tachycardia, increased heart rate, and changes in respiratory rate (NIAID, 2023).

151. NIAID conducted another challenge study to understand the effect of pre-existing immunity on disease progression. 76 healthy participants received a dose of 5x10⁶ TCID₅₀ of RG-A/Bethesda/MM2/H1N1 through an intranasal sprayer. There were no reported SAEs, however, some mild AEs were reported, including lymphadenopathy (13.16%), tachycardia (10.53%), a change in blood pressure (11.84%), and changes in respiratory rate (9.215%) (NIAID, 2021).

4.2.5 Shedding of virus from trial participants

152. Memoli et al. conducted a challenge study involving 46 healthy participants who received doses of the RG-A/CA/04/2009/H1N1 virus ranging from 103 to 107 TCID₅₀. Participants who received lower doses did not report any noticeable symptoms or viral shedding. The viral shedding was quantified using nasal swab by PCR. Symptoms and viral shedding were severe in participants who received 105 TCID₅₀ and higher. These patients started shedding the virus within 24–48 hours post-challenge, often 12–24 hours before the onset of symptoms and continued shedding for 4 to 5 days (Memoli et al., 2015).

153. NIAID conducted an influenza challenge study with 60 patients. In this study, 4 cohorts of patients received varying doses of RG-A/Texas/71/2017 (H3N2) ranging from 104 TCID₅₀ to 106 TCID₅₀. Viral shedding was determined using a qualitative RT-PCR on at least two days beginning 24 hours after the challenge until study day 8. The percentage of participants infected by the RG-A/Texas/71/2017 increased from 33.3% to 77.8% as the dose increased from 104 TCID₅₀ to 106 TCID₅₀. Viral shedding was investigated from day 1 to day 8 using nasopharyngeal (NP) swabs. None of the cohorts showed any detectable viral shedding at day 1, but around 20% of patients were shedding virus at day 8 (NIAID, 2023).

154. NIAID conducted another challenge study to understand the effect of pre-existing immunity on disease progression. 76 healthy participants received a dose of 5x10⁶ TCID₅₀ of RG-A/Bethesda/MM2/H1N1 through an intranasal sprayer. 23.7% of the volunteers were shedding the virus on day 8 confirmed by RT-PCR test from NP swabs ((NIAID), 2021).

155. There is limited or no shedding of viable influenza virus in human faeces following influenza infections, even though influenza RNA fragments can often be detected. Studies examining faecal samples from influenza-infected patients have concluded that faecal excretion of seasonal influenza viruses is unlikely to pose a major public health concern as the virus is only present when the dose is higher. The absence of viable influenza viruses in stools seems to indicate that intestinal cells cannot support the replication of seasonal influenza viruses (Chan et al., 2011; Minodier et al., 2019; Tamura et al., 2010; To et al., 2010).

156. Seasonal influenza viruses are rarely found in blood. An analysis of 28 blood samples donated from infected participants detected influenza A RNA in only one sample, but it is unclear if the virus was virulent. Viremia has been reported in patients with more virulent influenza strains, such as H5N1. A study by the American Red Cross examined 1,004 blood donors who later reported influenza symptoms and found no positive samples during the 2009 H1N1 outbreak. Other studies occurring during the same period confirmed no viral RNA in donors who developed symptoms 2 to 7 days after donation. In summary, influenza viruses are not transmitted through blood (CDC Yellow Book 2024; Dos Santos Bezerra et al., 2020).

157. Influenza viruses do not transmit through urine, so there is generally no chance of finding the virus in a urine sample. However, one reported case of the H1N1 pandemic virus was identified in a urine sample, which was confirmed using real-time reverse transcription-PCR (rRT-PCR). It remains unclear whether this detection was due to a fragment of viral RNA or a protein (Ho et al., 2013).

4.2.6 Transmissibility

158. A clear understanding of influenza transmission is essential for managing the risk of influenza infection. After the 2009 H1N1 pandemic, numerous studies have been conducted to understand the mode of influenza transmission. It is known that influenza replicates in epithelial cells throughout the respiratory system, including the upper and lower respiratory tract. As a result, the mouth and nose serve as the primary route of virus entry and exit.

159. However, a recent study has confirmed that the virus can also reach the nasopharynx via an ocular route (Bischoff et al., 2011). It is unlikely that influenza can transmit through faecal-oral or waterborne route (Minodier et al., 2019; Tamura et al., 2010; Webster et al., 1978).

160. A virus can infect a host if enough viruses survive the environment and reach the target cell. It also depends on factors such as the virus strain, the environment and characteristic of the host, which may all contribute to transmission (Figure 6).

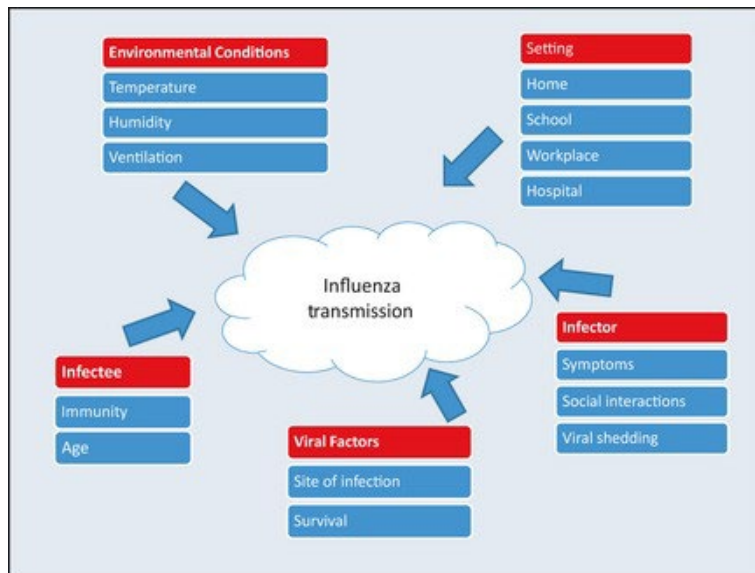


Figure 6: Factors that affect influenza transmission.

161. Influenza virus transmission is significantly influenced by the seasons, with outbreaks being more common in winter. Several factors contribute to this seasonal pattern. First, reduced exposure to sunlight in winter leads to decreased production of vitamin D, which can cause immune deficiency. Second, during the winter months, people tend to stay indoors more, facilitating the spread of the virus in closed environments. Finally, temperature and absolute humidity affect the survival of the influenza virus in the environment; low absolute humidity during winter is a key factor in influenza transmission, as supported by epidemiological data (Metz and Finn, 2015; Nguyen-Van-Tam et al., 2020).

162. Influenza virus can survive enough time on fomites and hands to transmit to the next host. However, uncertainties remain about how long it can survive outside of a host body. In general, the data support longer survival on hard (nonporous) surfaces than on softer (porous) items. Influenza A and B viruses survived for 24-48 hr on hard, nonporous surfaces such as stainless steel and plastic, 8-12 hr on cloth, paper, and tissues. Transmission could occur for 2-8 hr via stainless steel surfaces and for a few minutes via paper from a donor with a high viral load (Bean et al., 1982b). In addition, Influenza viruses become inactive in high temperatures and humid conditions (McDevitt et al., 2010).

163. Influenza can be transmitted through three mechanisms: bioaerosol (<5 µm), droplet (>10 µm), and contact transmission. The main mode of transmission among humans is through near-range inhalation of droplets or airborne spread. The virus can also be transmitted through direct contact with contaminated surfaces and subsequent administration on mucous membranes.

164. Teunis et al. developed a dose-response model combining data from twelve human challenge studies. They concluded both droplet and bioaerosols can produce a viral infection. Droplets carry a higher load, however, have a low chance of infection due to deposition in the upper respiratory tract. Bioaerosols can reach the lower respiratory tract, so there is a higher chance of infection,

however, the viral load is small. Despite equal infection risks, the corresponding risks of acute respiratory illness are somewhat higher for droplets due to the higher dose involved with larger particles (Teunis et al., 2010).

165. Influenza virus transmission can be prevented using PPE and personal hygiene practices. A large study was conducted in the UK to study influenza virus transmission in a challenge unit. Healthy, seronegative participant 'Donors' (n = 52) were randomly selected for intranasal challenge with influenza A. Groups of 'Recipients' who were randomised to Intervention (IR, n = 40) or Control (CR, n = 35) were exposed to Donors for four days. The intervention group wore face shields and hand sanitised frequently to limit large droplet and contact transmission. Only one transmitted infection was confirmed by serology in a control group recipient. Importantly, no transmission of infection was observed in the intervention (IR) group, which used controls of face masks, handwashing, and sanitising, similar to the proposed study (Nguyen-Van-Tam et al., 2020).

Section 5 Receiving environment

166. The receiving environment forms part of the context in which the risks associated with dealings involving the GMOs are assessed. Relevant information about the receiving environment includes the presence of species susceptible to the GMOs, the presence of the parent organism and related viral species, and environmental characteristics that may influence the likelihood of the GMOs spreading or persisting outside the site of release, or the harm they may cause.

5.1 The DCT facility

167. The patient bed and its surroundings will be the primary area for the maximum shedding and transmission of the virus, primarily due to the transmission pathway of influenza through droplets and aerosols. Other areas in the room, such as the door, toilets, and waste bins, may also be contaminated with influenza viruses.

168. The DCT facility would be equipped to handle infectious agents and procedures would be conducted in accordance with institutional policies based on standard precautions for handling potentially infectious substances and in accordance with the Australian Guidelines for the Prevention and Control of Infection in Healthcare (National Health and Medical Research Council, 2019).

5.2 Related viral species in the receiving environment

169. Human Influenza A and influenza B viruses are endemic in Australia, but their levels follow an annual pattern. Infections increase noticeably in May, peak between mid-July and mid-August, and subside in October or November.

170. Influenza viruses are part of the Orthomyxoviridae family, which is characterised by viruses with a segmented, negative-sense, single-stranded RNA genome. As there is no DNA intermediate, this family of viruses cannot integrate into the DNA genome of the host. The single-stranded RNA segments are not thought to be able to undergo homologous recombination. The segmented genome allows horizontal gene transfer through reassortment.

171. Reassortment only occurs with influenza viruses of the same type. Therefore, influenza A virus and influenza B virus do not reassort with each other, or with influenza C virus or with other Orthomyxoviridae. This is attributed in part to type specific virus packaging signals which are required for incorporation of a complete set of the 8 genomic RNA segments into virus particles (Baker et al., 2014; White et al., 2019). Incompatibilities between the polymerase subunit proteins between influenza A and B viruses may also contribute to the lack of reassortment between different influenza types (Wunderlich et al., 2010).

5.3 Similar genetic material in the environment

172. The GMOs are a copy of the wild-type virus. As a result, a large proportion of the Australian population has already been exposed to it.

173. In the latest Australian Respiratory surveillance report from September 2024, there were 8,336 influenza notifications. Of these, 86.9% (7,248/8,336) were influenza A (Unsubtyped), 8.6% (720/8,336) were influenza B, 3.6% (303/8,336) were influenza A(H3N2), and 0.7% (58/8,336) were influenza A(H1N1)(Australia).

5.4 Alternate hosts

174. Influenza viruses are obligate parasites, which cannot replicate outside a host as they depend on the host's proteins for many replicative processes. Influenza viruses are generally host specific.

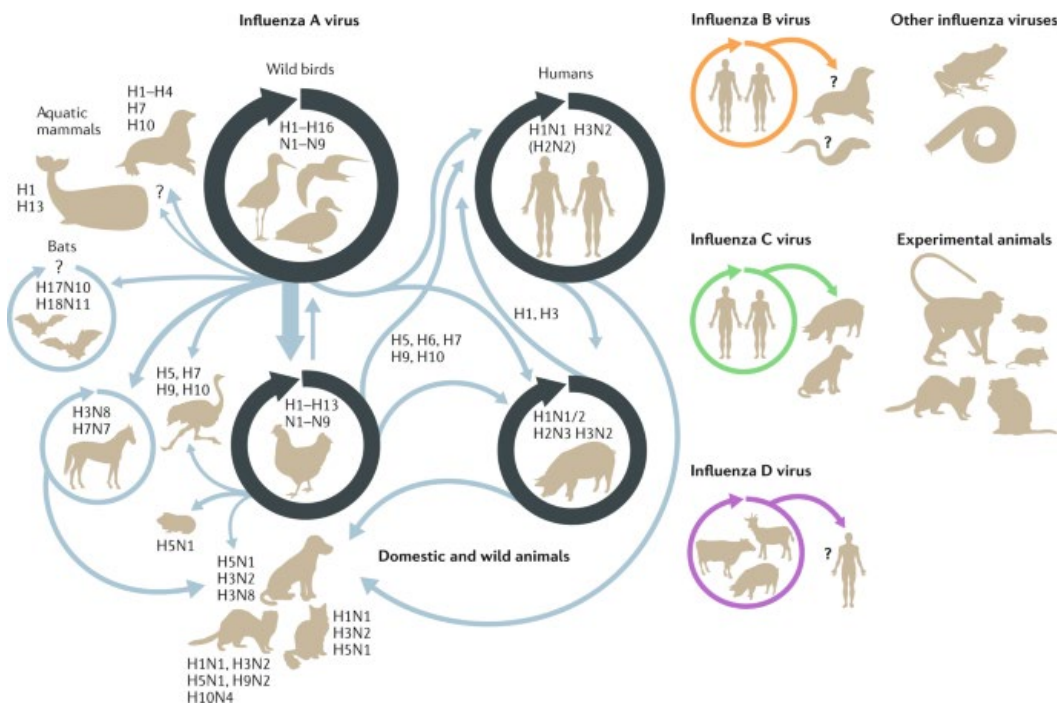


Figure 7: Ecology of influenza viruses

175. Influenza A virus (haemagglutinin (HA) subtypes 1–16) circulates in wild birds and can cross into different species via intermediate hosts and sometimes requiring adaptive mutations (light blue arrows; Figure 7). Specific subtypes predominate in certain species (dark blue circles; Figure 7). Influenza B viruses circulate in humans, although infections in seals have been described. Influenza C viruses circulate in humans and swine. The recently discovered influenza D viruses are found to circulate in cattle, goats and pigs (Long et al., 2019).

176. Guinea pigs and ferrets are the species most susceptible to wild-type human influenza A (Bouvier and Lowen, 2010), but are unlikely to be infected through shedding of the initial inoculum from an infected person. They are kept as pets but are neither farmed nor present in large numbers in Australia. Native birds and seals are less susceptible to wild-type human influenza viruses and therefore are unlikely to be infected through shedding of the GMO during trial.

177. Household animals can contract influenza, such as canine influenza, which is caused by the canine influenza virus. These canine influenza A viruses differ from the seasonal influenza A viruses that commonly circulate among humans. Almost all dogs are susceptible to dog flu infection. Dog flu

tends to spread among dogs housed in kennels and shelters. A small percentage of dogs can die from dog flu. Some dogs show no symptoms while others may become severely ill. To date, there is no evidence to suggest that canine influenza viruses can spread from dogs to people, and there have been no reported cases of human infection with a canine influenza virus anywhere in the world. Cats can be infected with influenza A viruses; however, it is unlikely to cause any significant illness in them (CDC, 2024).

178. It is well established that Influenza B only transmits to humans; however, some recent studies have been able to identify Influenza B in seals (Osterhaus et al., 2000).

Section 6 Relevant Australian and international approvals

6.1 Australian approvals

179. The proposed GMOs have not been studied previously in Australia.

180. However, the Regulator has previously issued DIR licences for similar dealings with other GM influenza vaccines such as DIR-171, a clinical trial using a GM influenza vaccine, with the test vaccine being imported and tested on up to 240 consenting volunteers in clinical facilities in Perth, Adelaide, Melbourne, Sydney, and Brisbane.

181. The Regulator issued a DIR licence (DIR 137) for the commercial supply of FluMist flu vaccines. Furthermore, the FluMist Quadrivalent influenza virus vaccine nasal spray developed by AstraZeneca Pty Ltd has been assessed and approved for use in Australia by the TGA and has been registered on the ARTG (ARTG ID: AUST R 244892) since 18 October 2016.

182. Additionally, the Regulator has approved clinical trials using GM CodaVax or other SAVE flu vaccines under a clinical trial DIR licence (DIR 144).

6.2 International approvals and experience

183. Clinical trials have been approved overseas using RG-influenza A virus (Table 4).

Table 4. Overseas approvals for clinical trials using RG-influenza virus

Study Number	Phase	Challenge Influenza Virus	Participant numbers	Countries	ClinicalTrials.gov or Eudra CT Identifiers
NCT04978454	I	A/Texas/71/2017/H3N2	96	United States	NCT02822105
NCT06476275	I	A/Texas/71/2017/ H3N2	recruiting, estimated enrolment 36	United States	NCT06476275
NCT04044352	I	A/Bethesda/MM2/H1N1	76	United States	NCT04044352
NCT02594189	I	A/Bethesda/MM1/H3N2	49	United States	NCT02594189
NCT01646138	I	A/CA/04/2009/H1N1	49	United States	NCT01646138
NCT02918006.	II	A/CA/like(H1N1)	179	United States	NCT01646138

Chapter 2 Risk Assessment

Section 1 Introduction

184. The risk assessment identifies and characterises risks to the health and safety of people or to the environment from dealings with GMOs, posed by, or as the result of, gene technology (Figure 8). Risks are identified within the established risk assessment context (Chapter 1), taking into account current scientific and technical knowledge. A consideration of uncertainty, in particular knowledge gaps, occurs throughout the risk assessment process.

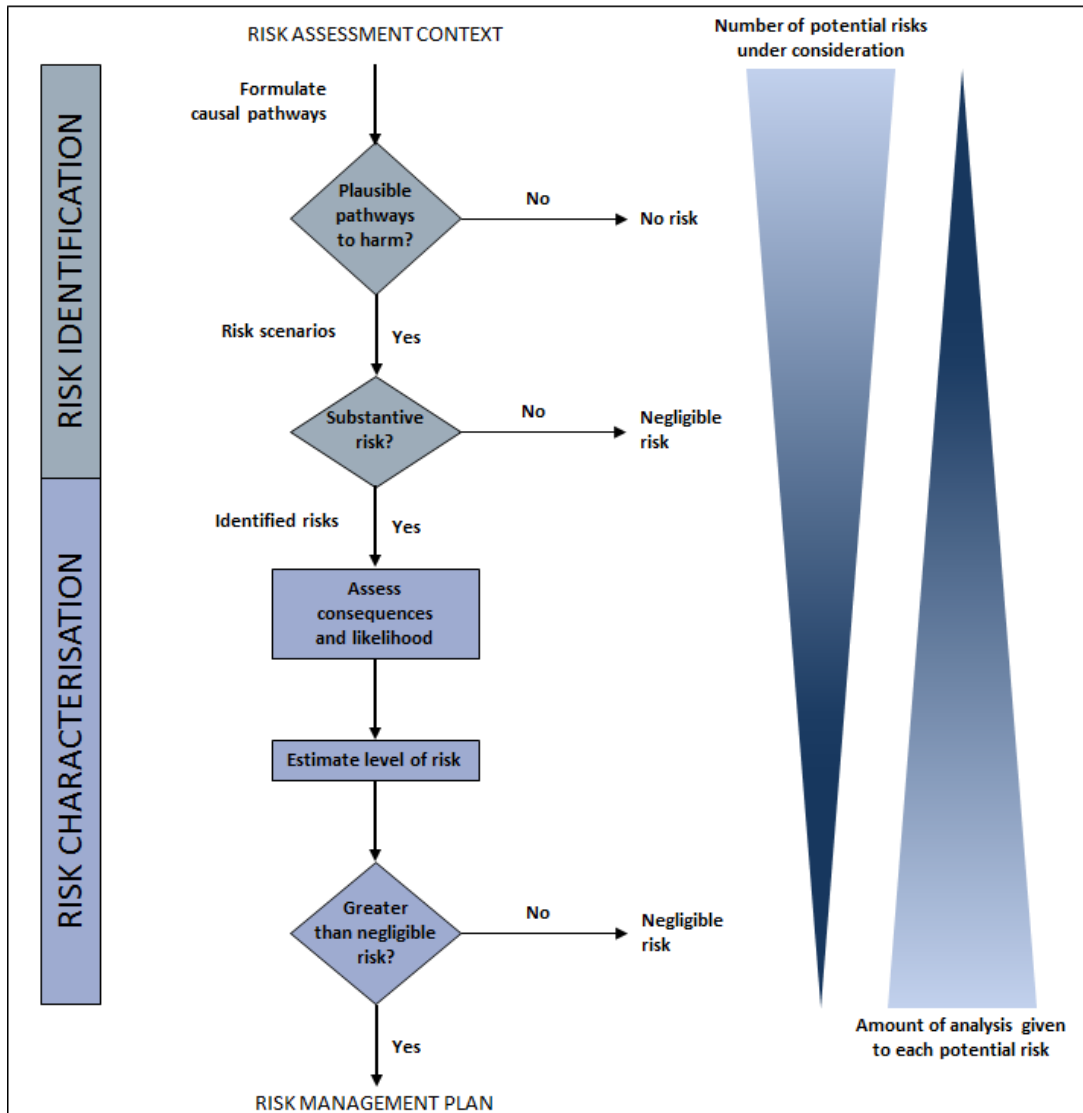


Figure 8. The risk assessment process

185. The Regulator uses a number of techniques to identify risks, including checklists, brainstorming, previous agency experience, reported international experience and consultation (OGTR, 2013).

186. Risk identification first considers a wide range of circumstances in which the GMO, or the introduced genetic material, could come into contact with people or the environment. This leads to postulating causal pathways that may give rise to harm for people or the environment from dealings with a GMO. These are risk scenarios.

187. Risk scenarios are screened to identify substantive risks, which are risk scenarios that are considered to have some reasonable chance of causing harm. Risk scenarios that could not plausibly occur, or do not lead to harm in the long or short term, do not advance in the risk assessment process (Figure 8), i.e. the risk is considered no greater than negligible.

188. Risk scenarios identified as substantive risks are further characterised in terms of the potential seriousness of harm (consequence assessment) and the likelihood of harm (likelihood assessment). The consequence and likelihood assessments are combined to estimate the level of risk and determine whether risk treatment measures are required. The potential for interactions between risks is also considered.

Section 2 Risk Identification

189. Postulated risk scenarios are comprised of three components (Figure 9):

- i. the source of potential harm (risk source)
- ii. a plausible causal linkage to potential harm (causal pathway), and
- iii. potential harm to people or the environment.

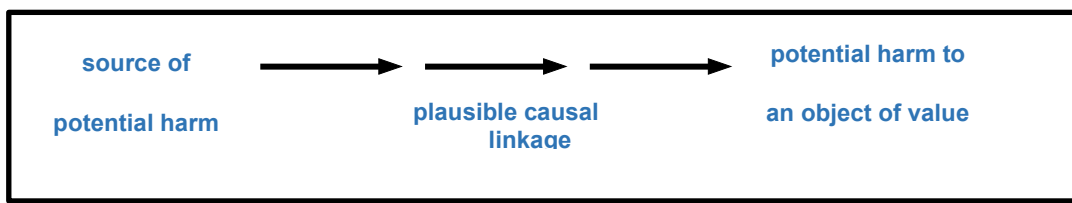


Figure 9. Components of a risk scenario

190. When postulating relevant risk scenarios, the risk context is taken into account, including the following factors detailed in Chapter 1:

- the proposed dealings
- the proposed limits including the extent and scale of the proposed dealings
- the proposed controls to limit the spread and persistence of the GMO and
- the characteristics of the parent organism(s).

2.1 Risk source

191. The parent organism is the respiratory pathogen, influenza virus A and B. Details on the pathogenicity and transmissibility of Influenza A and B virus is given in Chapter 1. Infection is generally the result of inhalation of aerosol droplets containing the virus or of mucosal exposure to contaminated surfaces. Disease symptoms include runny nose, fatigue, fever, cough and a sore throat and in some cases influenza infection can be fatal.

192. In this context, GMOs refer to influenza viruses that are produced by reverse genetics from wild-type influenza viruses' sequence. These GMOs can infect and replicate naturally in the human respiratory tract, like wild-type.

193. Infection with influenza viruses does not result in latent infection or integration into the host genome, and therefore, harm resulting from genetic recombination will not be considered further.

194. The eight-plasmid DNA transfection system is a widely recognised technique employed to generate GMOs. This method utilises multiple plasmids to introduce essential viral genes into host cells, ultimately producing a virus that retains the characteristics of the wild-type influenza virus. The GMO will be generated using a well-established and tested method in a facility located in the U.S., following current Good Manufacturing Practices (cGMP) and quality management. It is highly unlikely that a virus with novel traits will arise through this process. The applicant has stated that the GMOs will be tested to confirm they are not more pathogenic than the original parent organism. Therefore, harm resulting from GMO production will not be considered further.

195. Scientific studies have concluded that influenza viruses do not transmit through blood, urine, or faeces. Therefore, harm resulting from handling blood, urine, or faeces will not be considered further.

196. Influenza B do not transmit to another animal. Although household animals can contract influenza A, it causes minor illness. There is no reported case that house animals spread influenza A in human. Trial participants will remain in isolation for at least 7 days and are unlikely to come into contact with farm or wild animals and spread the virus due to the zoonotic barrier. Therefore, harm resulting from GMO transmission to animal will not be considered further (chapter 1 section 5.3).

197. Reassortment between different types of influenza viruses (e.g. A and B) does not occur and will not be considered further. Influenza viruses do not undergo homologous recombination as they have single-stranded RNA genomes. Reassortment between the GMO and a zoonotic influenza virus will not be considered further due to the unlikely occurrence of a co-infection and the presence of natural barriers to reassortment between divergent influenza viruses. Therefore, harm resulting from reassortment between influenza A and B will not be considered further.

198. The import, storage, and transport of GMO to and from the clinical trial facility and laboratory will be conducted under separate NLRDs. Only the risk associated with the transport of waste contaminated with GMOs will be considered.

2.2 Causal pathway

199. The following factors are taken into account when postulating plausible causal pathways to potential harm:

- the proposed dealings
- practices during and after administration of the GMOs
- the proposed limits including extent and scale of the proposed dealings
- the proposed controls to limit the spread and persistence of the GMOs
- potential exposure of other organisms to the GMOs in the environment
- spread and persistence of the GMOs (e.g. dispersal pathways and establishment potential)
- environmental stability of the organism (tolerance to temperature, UV irradiation and humidity)

- genetic mutation of the GMO.

200. Although all of these factors are taken into account, some are not included in the risk scenarios below as they may have been considered in previous RARMPs and a plausible pathway to harm could not be identified.

201. The trial sponsor, the Investigators and HREC all have roles in ensuring the safety of trial participants under the Therapeutic Goods Act 1989, and human clinical trials must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (National Health and Medical Research Council et al., 2018). Therefore, risk scenarios in the current assessment focus primarily on risks posed to people other than those participants in the trial, and to the environment.

202. The Act provides for substantial penalties for unauthorised dealings with GMOs or non-compliance with licence conditions, and also requires the Regulator to have regard to the suitability of an applicant to hold a licence prior to the issuing of the licence. These legislative provisions are considered sufficient to minimise risks from unauthorised activities. Therefore, unauthorised activities will not be considered further.

2.3 Potential harm

203. In addition, the following factors are taken into account when postulating relevant risk scenarios for this licence application:

- harm to the health of people or desirable organisms, including disease in humans or animals or adverse immune response
- the potential for establishment of a novel virus in the environment.

2.4 Postulated risk scenarios

204. Three risk scenarios were postulated and screened to identify any substantive risks. These scenarios are summarised in Table 4 and examined in detail in sections 2.4.1– 2.4.3 (this chapter).

205. In the context of the activities proposed by the applicant and considering both the short and long term, none of the risk scenarios gave rise to substantive risks.

Table 2. Summary of risk scenarios from the proposed dealings with the GMOs

Risk scenario	Risk source	Causal pathway	Potential harm	Substantive risk?	Reason
Risks to people undertaking dealings from exposure to GMOs					
1	GMO	Preparation and administration of the GMOs to trial participants via a nebuliser ↓ Exposure to staff undertaking dealings to GMO via: -exposure during GMO preparation for administration -direct contact with the trial participant - exposure to aerosolised secretions	Ill health	No	<p><u>Likelihood of exposure</u></p> <ul style="list-style-type: none"> • All dealings will be conducted by trained staff wearing appropriate PPE. • The staff will adhere to proper decontamination procedures within the trial room. <p><u>In the event of exposure</u></p> <ul style="list-style-type: none"> • DCT staff will be vaccinated against influenza. • DCT staff who are exposed to the GMO will receive antiviral medication.

Risk scenario	Risk source	Causal pathway	Potential harm	Substantive risk?	Reason
		<p>- contact with GMO contaminated items</p> <p style="text-align: center;">↓</p> <p>GMO transmits to appropriate infection site (respiratory tract)</p> <p style="text-align: center;">↓</p> <p>GMO replicates in respiratory epithelia cells</p> <p style="text-align: center;">↓</p> <p>Staff member develops Influenza infection</p>			<ul style="list-style-type: none"> • Accidental exposure would result in a dose much lower than that given to trial participants, insufficient to cause infection. • The GMOs are similar to circulating strains of influenza.
Risks to people and the environment from an unintentional release of GMOs					
2	GMO	<p>Administration of the GMOs to trial participants via a nebuliser</p> <p style="text-align: center;">↓</p> <p>Exposure of non-participant to GMO via:</p> <ul style="list-style-type: none"> -Participant withdraws from the trial and leaves the facility -Participant shedding virus post release - Participants are hospitalised -Exposure to GMO contaminated waste <p style="text-align: center;">↓</p> <p>GMO transmits to appropriate infection site (respiratory tract)</p> <p style="text-align: center;">↓</p> <p>GMO virus replicates into respiratory epithelia cell</p> <p style="text-align: center;">↓</p> <p>Non-participant develops Influenza infection</p>	Ill health	yes	<p>Influenza infection can cause severe illness, including hospitalisation and death among vulnerable individuals, thus posing a substantive risk. A detailed risk characterisation has been presented in section 3.1.1.</p>
3.	GMO	<p>Administration of the GMOs to trial participants via a nebuliser</p> <p style="text-align: center;">↓</p> <p>Viral replication in participant</p> <p style="text-align: center;">↓</p> <p>GMO virus gains novel trait via reassortment with seasonal influenza in participant</p> <p style="text-align: center;">↓</p> <p>Novel GMO infects host and replicates</p> <p style="text-align: center;">↓</p> <p>Establishment of viral infection</p> <p style="text-align: center;">↓</p> <p>Shedding of virus</p> <p style="text-align: center;">↓</p> <p>Risk scenario 1 and 2</p>	Ill health	Yes	<p>Influenza infection can cause severe illness, including hospitalisation and death among vulnerable individuals, thus posing a substantive risk. A detailed risk characterisation has been presented in section 3.1.2.</p>

2.4.1 Risk scenario 1

Risk source	GMO
Causal pathway	<p style="text-align: center;">Administration of the GMOs to trial participants via a nebuliser</p> <p style="text-align: center;">↓</p> <p style="text-align: center;">Exposure to staff undertaking dealings to GMO via:</p> <ul style="list-style-type: none"> -exposure during GMO preparation for administration -direct contact with the trial participant - exposure to aerosolised secretions - contact with GMO contaminated items <p style="text-align: center;">↓</p> <p style="text-align: center;">GMO transmits to appropriate infection site (respiratory tract)</p> <p style="text-align: center;">↓</p> <p style="text-align: center;">GMO replicates in respiratory epithelia cell</p> <p style="text-align: center;">↓</p> <p style="text-align: center;">Staff member develops Influenza infection</p>
Potential harm	Ill health

Risk source

206. The source of potential harm for this postulated risk scenario is the GMO (RG-influenza viruses).

Causal Pathway

207. This scenario applies to people conducting dealings at the DCT facility, during the collection and transport of waste, and to subsequent users of the treatment room (staff and/or patients). Distinct routes of exposure for each group are discussed below.

Exposure of people conducting dealings via inhalation of aerosolised GMO or airborne droplets

208. Clinical site staff treating participants with aerosolised GMO could inadvertently inhale it themselves.

209. The GMO will be transferred from a screw-cap vial to a syringe attached to an atomiser. During this procedure, there is a risk of accidental spillage or atomisation of the GMO, which could lead to exposure.

210. Participants will be admitted to the isolation facility and the GMO will be administered intranasally, 0.5 mL in each nostril (total 1mL) while lying supine, using the MAD Nasal™ Intranasal Mucosal Atomization.

211. MAD Nasal™ atomizes drugs into a fine mist of particles ranging from 30 to 100 microns, allowing them to reach and infect the epithelial cell line in the upper and lower respiratory tracts. DCT staff may be exposed to aerosolised spray due to accidental releases outside the nasal cavity. Additionally, patients may sneeze involuntarily during the administration because of irritation caused by the spray. These incidents could expose staff to a significant dose of the aerosol.

212. Sneezing and coughing is a common symptom of influenza and generates aerosolised droplets. As a result, DCT staff can be exposed to these aerosolised droplets while collecting samples, providing patient care, serving food, collecting waste and cleaning.

Exposure via contact with contaminated items or direct contact with the trial participant

213. Following administration, there are other ways a person conducting dealings within the facility can be exposed to the GMOs.

214. Participants will contaminate the isolation room by touching different surfaces, sneezing, coughing or leaving contaminated items (e.g., tissues, masks, etc.). DCT staff could be exposed to GMOs by contact transmission or inhaled air.

215. DCT staff will be collecting nasal swabs, exhaled air from the trial room, and blood, urine, and stool samples. Viable GMO may be present in the exhaled air or nasal swab. Influenza viruses do not transmit through blood, urine, and stool. Influenza viruses can survive in the environment depending on various factors (Chapter 1, Section 4.2.7). The proposed cleaning measures are likely to be sufficient to destroy any residual GMOs deposited on surfaces.

216. Contact with contaminated items is a major transmission pathway. DCT staff, including external service providers can touch contaminated surfaces or material (door handle, beds, food waste, tissues, etc.) and they could be exposed to the GMO through hand to mouth transmission of the virus. Exposure could occur during disposal materials contaminated with the GMO.

217. Previous clinical studies have shown that virus shedding can be detected within 24 hours post-administration and can continue for up to 10 days. Shedding of the GMOs is likely to occur through nasal excretion and saliva. Aside from sneezing and coughing, the GMOs may be found in used tissues or on surfaces contaminated with the GMOs as trial participants may contact those surfaces with contaminated hands. Persons conducting dealing could be exposed to the GMOs via this pathway.

In the event of an exposure

218. The clinical study with H3N2 (Chapter 1, Section 4.2.6) reveals that infection is dose-dependent. The percentage of participants infected by GMO increased from 33.3% to 77.8% as the dose increased from 104 TCID₅₀ to 106 TCID₅₀. This indicates that even the unlikely event that a DCT staff member is exposed to a full administration dose (106 TCID₅₀), the chance of infection is still only 77.8%. Additionally, the probability of infection decreases as the exposure dose decreases.

219. A UK study investigated the transmission of the influenza virus in a controlled setting where participants were divided into two groups. One group practiced hygienic behaviours (n=40), while the other group did not (n=35). In the second group, only one transmission occurred, suggesting that influenza transmission in a controlled environment is highly unlikely when preventive measures are implemented (Nguyen-Van-Tam et al., 2020). Therefore, it is highly unlikely that DCT staff or external service provider will be exposed to a dose that leads to infection.

220. In addition, all clinical staff preparing the GMO for administration and present in the room for administration of the GMO will be wearing PPE including disposable laboratory gowns, safety glasses, fit tested N95/P2 masks, disposable shoe coverings and disposable gloves. This will protect them from any aerosolised GMOs. In addition, the participant will be wearing a surgical mask after the administration to prevent transmission.

221. Participants will be accommodated in secure isolation rooms that feature individually vented and negative pressure airflow. Access to these rooms is restricted to authorised and trained staff, using a security swipe card. Participants will be segregated from one another and will have no contact with the public or any external people, except for clinical staff who will wear appropriate PPE. All dealings post-administration of the GMOs will be carried out by staff members wearing PPE

described earlier until shedding of the GMOs has ceased. This includes staff members serving food and carrying out the health checks and monitoring as required.

222. Specialist cleaners experienced in infectious units will be engaged to clean and disinfect isolation rooms in the DCT clinical unit. A record of the cleaners' names will be maintained. Cleaning will only commence 48 hours after a participant leaves the room, and full PPE will be required. All furniture and mattresses will be non-porous for easy disinfection. Bedding, pillows, and privacy curtains will be sanitised 48 hours post-departure, while contaminated laundry will be handled by trained waste contractors.

223. All waste (e.g., disposable containers, materials used on participants, general rubbish, food waste, vials with GMOs etc.) will be disposed of in a hands-free GMO waste bin. Mattresses, bedding, and linen will be decontaminated by a commercial laundry specializing in infection control. DCT will use a qualified GMO waste contractor to manage the off-site incineration of all GMO waste.

224. In an event where DCT staff or an external service provider is exposed to the GMO, it is highly unlikely that they will develop an active infection. For viruses to cause infection in new hosts, several prerequisites must be met: (i) they must survive in the environment; (ii) they must reach target cells in a new host; and (iii) enough virus must reach these target cells to achieve an infectious dose and initiate infection.

225. To ensure the safety and well-being, no vulnerable person will be included as a staff in this trial. All staff members engaged for this trial will have received the latest flu vaccination, minimising the risk of severe infection.

226. In addition, in the event that DCT staff are exposed to the GMOs, they will be confirmed through nasal swab RT-PCR testing and subsequently receive antiviral medication. This medication is reported to slow down transmission of the virus.

Potential harm

227. In healthy individuals, influenza typically causes mild infections, and most people recover without medication or major complications. The GMOs used in these clinical trials are no more pathogenic than influenza strains already circulating in the environment and therefore, it is highly unlikely that those viruses result in more severe infection than those already observed. DCT staff members will have received vaccination further reducing the consequences of severe influenza symptoms in the event they develop an infection.

Conclusion

228. Risk scenario 1 is not identified as a substantive risk because potential exposure routes to the GMO will be mitigated by the proposed controls, and the GMO is similar to circulating strains of influenza already in the environment. It is highly unlikely that the DCT staff, including external service providers, will be exposed to RG viruses that could lead to infections. As DCT staff would receive vaccination and unlikely to be vulnerable individual, the consequence of a staff members is infected would range from marginal to minor. Therefore, this risk could not be greater than negligible and does not warrant further detailed assessment.

2.4.2 Risk scenario 2

229. Risk Scenario 2 considers the potential harm to vulnerable people exposed to the GMO. As Risk Scenario 2 is considered to be a substantive risk, a risk characterisation was conducted as detailed in Section 3.

2.4.3 Risk scenario 3

230. Risk Scenario 3 considers the potential harm to vulnerable people exposed to a reassorted GMO. As Risk Scenario 3 is considered to be a substantive risk, a risk characterisation was conducted as detailed in Section 3.

Section 3 Risk characterisation

231. Three risk scenarios were postulated and evaluated, as summarised in Table 4. The second and third risk scenario was identified as posing a substantive risk which warrants further assessment. This section provides more detail on the evaluation of this scenario.

3.1.1 Risk Scenario 2. Transmission of the GMO to non-participant

Risk source	GMO
<p>Causal pathway</p>	<p style="text-align: center;">Administration of the GMOs to trial participants via a nebuliser</p> <p style="text-align: center;">↓</p> <p style="text-align: center;">Exposure to non-participant to GMO via:</p> <ul style="list-style-type: none"> -Participant withdraws from the trial and leaves the facility -Participant shedding virus post release - Participants are hospitalised -Exposure to GMO contaminated waste <p style="text-align: center;">↓</p> <p style="text-align: center;">GMO transmits to appropriate infection site (respiratory tract)</p> <p style="text-align: center;">↓</p> <p style="text-align: center;">GMO virus replicates into respiratory epithelia cell</p> <p style="text-align: center;">↓</p> <p style="text-align: center;">Non-participant develops Influenza infection</p>
<p>Potential harm</p>	<p style="text-align: center;">ill health</p>

Risk source

232. The source of potential harm for this postulated risk scenario is the GMO (RG-influenza viruses).

Causal Pathway

233. This scenario applies to exposure of other people than those conducting dealings to the GMO as the result of the release of the GMOs outside the DCT facility. A non-participant, such as a close contact of a trial participant, staff member at a waste disposal site, and ambulance/hospital staff could be exposed to GMO in several ways.

Release of the GMOs outside of the DCT facility

234. There is a possibility that trial participants can shed GMOs after being released from the DCT trial facility at the end of their stay. As mentioned earlier, clinical studies have established that shedding can last for 8 to 11 days. The applicant proposed that trial participants will be tested for the GMO on day 6. If they test positive for the GMO, they will receive an antiviral treatment. All trial participants would be released on day 7 either negative for the GMO or having received an antiviral treatment in the last 24 hours, therefore minimising the spread of the GMO outside the DCT facility.

235. It is possible that a participant in the clinical trial develops a severe adverse event requiring hospitalisation. There is a potential risk that the ambulance crew could be exposed to the GMOs through coughing, sneezing, and bodily discharge from respiratory tract via contact. The hospital staff and patients could come into contact with the hospitalised participant and be exposed to the GMOs.

236. A participant could potentially withdraw from the study at any time, including while suffering from an active infection and potentially spread it within the community. Clinical data indicates that participants begin shedding the virus within 24 hours of administration, and this shedding can last for 8 to 11 days. Trial participants must sign a consent form outlining the clinical trial procedures, potential risks, and their obligations. If a participant withdraws from the trial and leaves the isolation room, they will be offered antiviral medication and will be advised to wear a mask for 48 hours. Additionally, they are advised to isolate at home to limit the spread of the virus. However, they could withdraw consent at any time and refuse to follow those recommendations. One of the exclusion criteria for the enrolment of participant is that selected participants must not have any household contacts that are at higher risk for influenza-related complications including persons ≥ 65 years of age or < 5 years of age, and pregnant individuals

237. The participants in this clinical trial will be healthy volunteers with a baseline level of immunity to infection. Exclusion criteria are in place to prevent vulnerable individuals from participating in the trial. Therefore, it is highly unlikely that a participant will require hospitalisation. In the highly unlikely event that a participant experiences a severe reaction or a medical emergency during the trial and requires transfer to a hospital, a special arrangement has been made with the Royal Melbourne Hospital for participants to be accommodated in Pod D of their ICU unit. This area is equipped with the necessary facilities and staff who will follow the Viral Hemorrhagic Fever Protocols for infection. In the event of hospitalisation, both the participant and the ambulance staff will be equipped with full personal protective equipment (PPE) during transit. The ambulance personnel will be fully briefed on the participant's health status, including the administration of a GMO. Additionally, waste generated during the transfer and treatment at the Royal Melbourne Hospital will be disposed of according to the Regulator's *Guidelines for Transport, Storage and Disposal* (TSD), which are in line with Viral Hemorrhagic Fever infection control protocols.

238. As described in risk scenario 1, in a situation where a non-participant is exposed to the GMOs, it is very unlikely that they will develop an active infection. For viruses to infect new hosts, several conditions need to be fulfilled: (i) they must endure in the environment; (ii) they must access target cells in a new host; and (iii) a sufficient quantity of virus must reach these target cells to create an infectious dose and trigger an infection.

239. The environment significantly influences the transmission of influenza. During the summer, high temperatures and increased humidity will inactivate the virus, resulting in a lower incidence of flu during that season. Therefore, it is unlikely that GMOs will spread in the summer. In contrast, during the winter, the risk of transmission is higher. However, many people will be vaccinated or have acquired immunity through previous influenza infections, making them less vulnerable to influenza infection and less likely to subsequently transmit the virus at infectious doses if they do become infected due to lower viral loads.

240. The human body has innate immunity against the influenza virus through various mechanisms. The viral RNA present within infected cells is recognised as foreign by several pattern recognition receptors (PRRs), which activates an immune response that helps prevent further viral infection (Iwasaki and Pillai, 2014). Therefore, a healthy person exposed to the GMOs, who has previously been infected or vaccinated against Influenza, is likely to have pre-existing immunity against influenza A or B, minimising the risks of severe infection. Additionally, from time to time, the advice provided by WHO, regarding the influenza strain selected for the development of influenza vaccines, have been incorrect; however, studies have found that even if the influenza vaccine does not target the precise strain of influenza they are generally effective against influenza viruses (Tricco et al., 2013). Given the similar nature of seasonal influenza, these vaccines should also be effective against GMOs.

Consequence assessment

241. Influenza is a viral infection that affects the respiratory tract and can lead to a variety of symptoms. These symptoms include fever or chills, cough, sore throat, runny or stuffy nose, muscle aches, headaches, and fatigue. Children may also experience vomiting and diarrhoea. The severity of influenza can depend on several factors, including underlying health conditions, age, a weakened immune system, pregnancy, and lifestyle.

Influenza infection with marginal to minor consequences

242. Most healthy individuals typically recover from the flu within one to two weeks. During this time, they may experience mild symptoms for a few days. Common symptoms of the flu include a high fever, chills, a sore throat, and nasal congestion or a runny nose. While these symptoms can be unpleasant, they generally resolve on their own without the need for extensive medical treatment. Therefore, the consequence for a healthy person exposed to the GMOs resulting in an infection would only range from marginal to minor.

Influenza infection with marginal to major consequences

243. Individuals at higher risk from influenza infection include pregnant women, young children (< 5 years), adults aged 65 years and older, individuals with underlying chronic medical conditions, and Aboriginal or Torres Strait Islander people. One of the exclusion criteria for the enrolment of participant is that selected participants must not have any household contacts who are at higher risk for influenza-related complications including persons ≥ 65 years of age or < 5 years of age, and pregnant individuals. This exclusion criteria further minimise the consequences of exposure to the GMO by a person more vulnerable to the virus.

244. As mentioned in Chapter 1 section 3.1, for this class of more vulnerable people, exposure to the GMOs resulting in an infection could lead to marginal consequences, where infection results in with very little symptoms, but could also develop into more severe symptoms requiring hospitalisation and in some extreme circumstances, death could occur. This would be a major consequence.

Risk estimate

245. The risk estimate is based on a combination of the likelihood and consequence assessments, using the Risk Estimate Matrix as described in the Regulator's Risk Analysis Framework 2013.

246. The potential consequences of GMOs on healthy individuals are marginal to minor, with a highly unlikely probability. Therefore, the overall risk is estimated to be negligible.

247. The potential consequence of a vulnerable person being infected by a GMO is considered to be marginal to major; however, this event is highly unlikely. Therefore, the overall risk is estimated to be negligible to moderate.

3.1.2 Risk scenario 3

Risk source	GMO
Causal pathway	Administration of the GMOs to trial participants via a nebuliser ↓ Viral replication in participant ↓ GMO virus gains novel trait via reassortment with seasonal influenza in participant ↓ Novel GMO infects host and replicates ↓ Establishment of viral infection ↓ Shedding of virus ↓ Risk scenario 1 and 2
Potential harm	Ill health

Risk source

248. The source of potential harm for this postulated risk scenario is the reassorted GM influenza virus.

Causal pathway

249. This scenario applies to a trial participant being administered a GMO and, the GMO transducing a cell already transduced with another influenza strain and reassortment could result in viral progeny having any permutation of the possible combinations of the genomic segments from the parental viruses and could gain novel trait. The novel virus could then be shed from the recombination host and transmitted to other hosts in the environment.

250. Co-infection in trial participants could occur if the trial participant has an existing influenza infection at the time of administering the GMO, or if the trial participant acquired an influenza infection while the GMO is present.

251. The applicant has proposed that only healthy trial participants take part in the clinical trial. A participant could be infected with a seasonal influenza strain immediately prior to entering the clinical trial. However, participants will be admitted two days before the clinical trial begins, making it very unlikely that both the GMOs and the seasonal influenza strain will infect the host cell simultaneously, which is critical for reassortment to occur. Additionally, all participants will be tested for any active infections.

252. Another possible scenario is that a participant leaves the clinical trial with an active infection and subsequently contracts a seasonal influenza strain. However, this is also considered a highly unlikely event.

253. Reassortment between GMOs and a second strain of influenza can occur during vaccine challenge studies. In a vaccine challenge study, a participant receives an influenza vaccine and is then admitted after a certain period to receive the GMO to test the vaccine's effectiveness. Reassortment could occur between the GMO and the vaccine if the vaccine tested is a live vaccine. The applicant

has not stated the time elapsed between the administration of the vaccine and the challenge with the GMO. It is to be noted in this instance, that it is likely that the administered vaccines would be via intramuscular or subcutaneous injection, while the challenge with the GMO would occur via a nebuliser. It is therefore highly unlikely that those two influenza strains would be found in the same location within the participant, resulting in a highly unlikely event to occur.

254. DCT staff members will receive the influenza vaccine and are trained professionals, making it improbable that they will come into contact with trial participants if they have an active influenza infection.

255. As discussed in chapter 1, section 3.6, co-infection of a host cell by a second influenza virus is strongly inhibited in a time-dependent manner both in vivo and in vitro. This results in a small temporal window where co-infection with two influenza viruses can occur. Together, these data suggest that there is a limited, small temporal window where co-infection with the GMO and a circulating virus could occur.

Consequence assessment

256. In the event a recombinant influenza strain is produced, the resulting reassortant would not be any more pathogenic than either of the strains. Reassortment between two circulating strain of influenza A or B is not expected to result in an influenza virus more virulent or with a different host range. Therefore, the consequence would remain similar than those assessed in risk scenario 1 and 2. The worst-case scenario would be the exposure to the reassortant virus to a person outside the DCT trial site more susceptible to influenza infection, such as a senior citizen, young children and pregnant or breastfeeding people. The consequence would range from marginal to major in the event an exposure resulting in an infection occurs.

Risk estimate

257. The potential consequences of a recombinant influenza strain on healthy individuals are marginal to minor, with a likelihood of highly unlikely. Therefore, the overall risk is estimated to be negligible.

258. The potential consequence of a vulnerable person being infected by a recombinant influenza strain is marginal to major; however, this event is highly unlikely. Therefore, the overall risk is estimated to be negligible to moderate.

Section 4 Uncertainty

259. Uncertainty is an intrinsic part of risk analysis and is present in all aspects of risk analysis. This is discussed in detail in the Regulator’s Risk Analysis Framework document.

260. Uncertainty is addressed by approaches such as balance of evidence, conservative assumptions, and applying risk management measures that reduce the potential for risk scenarios involving uncertainty to lead to harm. If there is residual uncertainty that is important to estimating the level of risk, the Regulator will take this uncertainty into account in making decisions.

261. As clinical trials are designed to gather data, there are generally data gaps when assessing the risks of a clinical trial application involving GMOs. However, clinical trial applications are required to be limited and controlled. Even if there is uncertainty about the characteristics of a GMO, limits and controls restrict exposure to the GMO, and thus decrease the likelihood of harm.

262. For DIR-210, there is uncertainty regarding participants withdrawing from the trial before completing the trial. In the event a participant chooses to leave the clinical trial facility, they will be provided with antiviral medication and advised to remain in isolation for 48 hours. It is uncertain whether participants will comply with this advice. While some uncertainty remains regarding participants' behaviour after leaving the clinical trial facility, it is unlikely that this will pose additional risks. Risk scenario 2 considers the risk associated with withdrawal from the clinical trial and licence conditions have been imposed to reduce the risk to people.

263. As discussed in Chapter 1, the influenza virus evolves randomly, which always leaves a margin of uncertainty regarding the virulence of GMOs. These viruses can potentially gain new traits during production or through reassortment throughout the clinical trial. However, the likelihood of reassortment occurring is very low due to the limits and controls in place. Furthermore, it is highly unlikely that this will lead to serious consequences such as hospitalization or community spread, as the DCT has implemented proper methods to prevent such scenarios. Additionally, influenza viruses already present in the Australian population mean that the risk associated with the emergence of a novel virus is similar.

264. Overall, the level of uncertainty in this risk assessment is considered low and does not impact on the overall estimate of risk.

Section 5 Risk evaluation

265. Risk is evaluated against the objective of protecting the health and safety of people and the environment to determine the level of concern and, subsequently, the need for controls to mitigate or reduce risk. Risk evaluation may also aid consideration of whether the proposed dealings should be authorised, need further assessment, or require collection of additional information.

266. Factors used to determine which risks need treatment may include:

- risk criteria
- level of risk
- uncertainty associated with risk characterisation
- interactions between substantive risks.

267. Three risk scenarios were postulated whereby the proposed dealings might give rise to harm to people or the environment. Those scenarios considered the risk of exposure to the GMO of people conducting dealings and also people outside the DCT facility. A risk scenario also considered the risk associated with reassortment of the GMO with a live attenuated vaccines used in the challenge study or a naturally circulating strain of the virus.

268. A risk is only identified as substantive when a risk scenario is considered to have some chance of causing harm. Risk scenarios that do not lead to harm, or could not reasonably occur, do not represent an identified risk and do not advance any further in the risk assessment process. In the context of the control measures proposed by the applicant, two of the three risk scenarios were identified as a substantive risk requiring further assessment.

269. The GMOs are genetically and phenotypically similar to the wild-type viruses circulating in the Australian population. The risks are identical than those associated with the exposure to a non-GM circulating strain of influenza. The risk associated with the exposure to the GMO of people outside of the DCT facility and the risk associated with reassortment was estimated as negligible to moderate.

Additional treatment measures to mitigate the identified risks should be applied and are considered in chapter 3.

270. The limits and controls proposed by the applicant are suitable for addressing the risks associated with the proposed dealings with the GMO. However, in order to maintain the risk context in which the release of the GMO into the environment is limited and controlled, conditions are imposed in the licence. The Regulator considers that the dealings involved in this proposed release do not pose a significant risk to either people or the environment.¹

¹ As none of the proposed dealings are considered to pose a significant risk to people or the environment, Section 52(2)(d)(ii) of the Act mandates a minimum period of 30 days for consultation on the RARMP.

Chapter 3 Risk management plan

Section 1 Background

271. Risk management is used to protect the health and safety of people and to protect the environment by controlling or mitigating risk. The risk management plan addresses risks evaluated as requiring treatment and considers limits and controls proposed by the applicant, as well as general risk management measures. The risk management plan informs the Regulator’s decision-making process and is given effect through licence conditions.

272. Under Section 56 of the Act, the Regulator must not issue a licence unless satisfied that any risks posed by the dealings proposed to be authorised by the licence are able to be managed in a way that protects the health and safety of people and the environment.

273. All licences are subject to three conditions prescribed in the Act. Section 63 of the Act requires that each licence holder inform relevant people of their obligations under the licence. The other statutory conditions allow the Regulator to maintain oversight of licensed dealings: Section 64 requires the licence holder to provide access to premises to OGTR inspectors and Section 65 requires the licence holder to report any information about risks or unintended effects of the dealing to the Regulator on becoming aware of them. Matters related to the ongoing suitability of the licence holder are also required to be reported to the Regulator.

274. The licence is also subject to any conditions imposed by the Regulator. Examples of the matters to which conditions may relate are listed in Section 62 of the Act. Licence conditions can be imposed to limit and control the scope of the dealings. In addition, the Regulator has extensive powers to monitor compliance with licence conditions under Section 152 of the Act.

275. Licence conditions are discussed and summarised in this Chapter and listed in detail in the licence.

Section 2 Risk treatment measures for substantive risks

276. The risk identification process led to identification of two substantive risks, involving the exposure to people outside the clinical facility and the production of a novel strain of influenza as a result of reassortment. These risks were characterised in Chapter 2, section 3 and risk evaluation proposed that these risks should be treated.

277. The applicant has proposed several limits and controls to prevent exposure to vulnerable people (details Chapter 1, section 2.1). These include:

- The applicant has proposed to exclude trial participants who have close contact with vulnerable people including persons ≥ 65 years of age or < 5 years of age, and pregnant individuals. This is included in the draft licence.

- DCT has established a facility dedicated to supporting early-phase infectious disease clinical studies. The DCT facility features a purpose-built Clinical Ward Area with six (6) secure isolation rooms. Rooms are on the second floor of the building, only accessible by authorised and trained staff using a security swipe card. All study activities during this period, including participant monitoring and sample collection, will be conducted within these secure isolation rooms. This will prevent exposure to non-trial participants. A condition is included in the licence to require that all trials must be conducted at the DCT facility and all dealings with the GMO to be conducted within these rooms, in particular, the administration of the GMOs to trial participants. These rooms must also operate at negative pressure in relation to the common areas while the GMO is administered.

-The applicant advised that appropriate PPE should be worn when entering isolation rooms, including wearing a gown, gloves, overshoes, goggle and face mask. Clinical trial staff performing dealings with the GMO including administration of the GMO to trial participants and clean-up of potential spills would wear PPE. All the staffs and external service providers will also follow donning and doffing procedures. A condition is also included in the licence to ensure all PPE except for the N95 mask is removed prior leaving the facility. The door handle and hands must also be decontaminated prior exiting the isolation rooms. A condition is also included to ensure those rooms are equipped with appropriate disinfectant and GMO-labelled bins. This is to minimise the risk of contamination of common areas where staff are unlikely to wear PPE.

278. The applicant proposed participants must sign a consent form outlining the clinical trial procedures, potential risks, and their obligations. A condition is included in the licence requiring the licence holder to obtain written approval from the trial participant that they will remain at the trial site for at least 7 days, agree to receive antiviral treatment, if required, and isolate and avoid susceptible people if found to be positive on day 7.

279. A licence condition is included to ensure all DCT staff members are vaccinated and aware of the potential risk associated with exposure to the GMO for vulnerable people, including pregnant and breastfeeding people.

Section 3 General risk management

280. The limits and controls proposed in the application were important in establishing the context for the risk assessment and in reaching the conclusion that the risks posed to people and the environment are negligible. Therefore, to maintain the risk context, licence conditions have been drafted to limit the clinical trial to the proposed size, location and duration, and to restrict the spread and persistence of the GMO and its genetic material in the environment. The conditions are discussed and summarised in this Chapter and listed in detail in Chapter 4 (the draft licence).

3.1 Limits and controls on the clinical trial

281. Sections 2.1 and 2.2 in Chapter 1 list the limits and controls proposed by DCT. Many of these are discussed in the three risk scenarios considered in Chapter 2 and listed in Chapter 3, section 2. The appropriateness of the limits and controls is considered further in the following sections.

3.1.1 *Consideration of limits and controls proposed by DCT*

282. In the proposed clinical trial, the maximum number of participants will be 150 over the course of this licence. Studies will be conducted with groups of 6 to 12 participants at a time, with each participant receiving only a single dose of the GMO. This approach will limit the exposure of DCT staff (Risk Scenario 1). A licence condition is included to limit the number of participants enrolled under this licence.

283. The trial will be held in a dedicated DCT clinical trial facility to support early-phase infectious disease studies. A licence condition restricting the conduct of dealings at this site is included.

284. Participants in the trial will be limited to healthy individuals, and the relevant proposed inclusion and exclusion criteria are outlined in Chapter 1, Section 2.3.3. These criteria will be subject to approval by a HREC, which will consider the safety of individuals involved in the trial. This aims to minimise the potential for the spread and persistence of the GMOs

285. Participants will receive the GMO via nasal administration, performed by trained clinical staff in the DCT clinical trial facility. Participants will also wear surgical masks for an additional 1.5 hours after administration to limit the spread of droplets and aerosols.

286. Licence conditions will require that only participants willing to comply with the clinical trial protocol be included, and they must be briefed about the consequences of early withdrawal from the trial.

287. Conditions are included in the draft licence requiring the licence holder to ensure that all GMOs, including material or waste that has been in contact with the GMOs are decontaminated by autoclaving, chemical treatment or by high-temperature incineration. Disposal of GMOs, other than by external service providers, must be in accordance with Regulator's *Guidelines for the Transport, Storage and Disposal* of GMOs for PC2 GM microorganisms. Draft licence conditions are included to reflect this. The draft licence also requires waste disposal by external service providers to be by autoclaving or incineration.

288. A standard condition is included in the draft licence requiring the licence holder to ensure that dealings are conducted so as to ensure containment of the GMO, not compromise the health and safety of people and minimise unintentional exposure to the GMO.

289. Further conditions have also been included in the draft licence to ensure that a Compliance Management Plan is provided to the Regulator before administration of each GMO variant commences. The Compliance Management Plan must provide information including the detail of the GMO, the number of participants enrolled, the type of study conducted and the expected date of administration.

3.1.2 Summary of draft licence conditions to be implemented to limit and control the clinical trial

290. A number of licence conditions have been drafted to limit and control the proposed clinical trial, based on the above considerations. These include requirements to:

- limit the trial up to 150 trial participants at DCT in isolation rooms
- ensure personnel involved in the trial are appropriately trained and follow appropriate behavioural requirements
- ensure appropriate PPE is used inside the DCT isolation rooms
- restrict personnel permitted to administer the GMO.

3.2 Other risk management considerations

291. All DIR licences issued by the Regulator contain a number of conditions that relate to general risk management. These include conditions relating to:

- applicant suitability
- contingency plans
- identification of the persons or classes of persons covered by the licence
- reporting requirements
- access for the purposes of monitoring for compliance.

3.2.1 Applicant suitability

292. In making a decision whether or not to issue a licence, the Regulator must have regard to the suitability of the applicant to hold a licence. Under Section 58 of the Act, matters that the Regulator must take into account include:

- any relevant convictions of the applicant
- any revocation or suspension of a relevant licence or permit held by the applicant under a law of the Commonwealth, a State or a foreign country
- the capacity of the applicant to meet the conditions of the licence.

293. If a licence were issued, the conditions would include a requirement for the licence holder to inform the Regulator of any information that would affect their suitability.

294. In addition, the applicant organisation must have access to an IBC and be an accredited organisation under the Act.

3.2.2 Contingency Plans

295. If a licence were issued, DCT has provided a contingency plan in the event of a spill but also in the event a staff member is exposed and develops flu-like symptoms.

3.2.3 Identification of the persons or classes of persons covered by the licence

296. If a licence were issued, the persons covered by the licence would be the licence holder and employees, agents or contractors of the licence holder and other persons who are, or have been, engaged or otherwise authorised by the licence holder to undertake any activity in connection with the dealings authorised by the licence.

3.2.4 Reporting requirements

297. If issued, the licence would require the licence holder to immediately report any of the following to the Regulator:

- any additional information regarding risks to the health and safety of people or the environment associated with the dealings
- any contraventions of the licence by persons covered by the licence
- any unintended effects of the clinical trial.

298. A number of written notices would also be required under the licence regarding dealings with the GMO, to assist the Regulator in designing and implementing a monitoring program for all licensed dealings. The notices would include:

- expected date of administration with the GMOs
- cease of administration with GMOs at this site.

3.2.5 Monitoring for Compliance

299. The Act stipulates, as a condition of every licence, that a person who is authorised by the licence to deal with a GMO, and who is required to comply with a condition of the licence, must allow inspectors and other persons authorised by the Regulator to enter premises where a dealing is being undertaken for the purpose of monitoring or auditing the dealing.

300. If monitoring activities identify changes in the risks associated with the authorised dealings, the Regulator may also vary licence conditions, or if necessary, suspend or cancel the licence.

301. In cases of non-compliance with licence conditions, the Regulator may instigate an investigation to determine the nature and extent of non-compliance. The Act provides for criminal sanctions of large fines and/or imprisonment for failing to abide by the legislation, conditions of the licence or directions from the Regulator, especially where significant damage to the health and safety of people or the environment could result.

Section 4 Issues to be addressed for future clinical trials or commercial release

302. Additional information has been identified that may be required to justify a reduction in limits and controls. This includes information and data that would address the uncertainties noted in Chapter 2 section, such as the likelihood of the GMOs evolving during a particular trial and becoming more virulent.

Section 5 Conclusions of the consultation RARMP

303. The RARMP determined that the proposed clinical trial presents negligible to moderate risks to the health and safety of individuals. Licence conditions have been proposed to mitigate the risks associated with this clinical trial. In addition, since this is a clinical trial, the licence includes limits on the number of trial participants, types of facilities used, exclusion criteria, and as well as a range of controls to minimise the potential for exposure of people other than trial participants, to the GMO. There are also several general conditions relating to ongoing licence holder suitability, auditing and monitoring, and reporting requirements, including an obligation to report any unintended effects.

Chapter 4 Draft Licence Conditions

Section 1 Interpretations and Definitions

1. In this licence:

- (a) unless defined otherwise in this licence, words and phrases used in this licence have the same meaning as they do in the Act and the Gene Technology Regulations 2001;
- (b) words importing a gender include every other gender;
- (c) words in the singular number include the plural and words in the plural number include the singular;
- (d) expressions used to denote persons generally (such as “person”, “party”, “someone”, “anyone”, “no one”, “one”, “another” and “whoever”), include a body politic or corporate as well as an individual;
- (e) references to any statute or other legislation (whether primary or subordinate) are a reference to a statute or other legislation of the Commonwealth of Australia as amended or replaced from time to time and equivalent provisions, if any, in corresponding State law, unless the contrary intention appears;
- (f) where a word or phrase is given a particular meaning, other grammatical forms of that word or phrase have corresponding meanings;
- (g) specific conditions prevail over general conditions to the extent of any inconsistency.

2. In this licence:

‘Act’ means the *Gene Technology Act 2000* (Commonwealth) or the corresponding State law under which this licence is issued.

‘Analytical facility’ means a laboratory in Australia accredited to undertake testing of human diagnostic Samples, such as a medical testing laboratory accredited by the National Pathology Accreditation Advisory Council (NPAAC).

‘Clinical trial site’ means Doherty Clinical Trials clinical trial facility located at 2 St Andrews Place, East Melbourne, Victoria 3002.

‘Decontaminate’ (or **‘Decontamination’**) means, as the case requires, kill the GMOs by one or more of the following methods:

- (a) chemical treatment;
- (b) autoclaving;
- (c) high-temperature incineration; or
- (d) a method approved in writing by the Regulator.

Note: 'As the case requires' has the effect that, depending on the circumstances, one or more of these techniques may not be appropriate.

'Excluded persons' means:

- Persons with household contacts at higher risk for influenza-related complications, including persons ≥ 65 years of age or < 5 years of age, history of chronic pulmonary disease or pregnant person;
- persons who display any evidence of an active infection with influenza viruses;
- persons who are breastfeeding or who are pregnant.

'External service provider' means a person engaged by the licence holder solely in relation to transport, storage and/or disposal of the GMOs, and who is not undertaking any dealings with the GMOs that are not for those purposes.

'GM' means genetically modified.

'GMO' means the genetically modified organisms that are the subject of the dealings authorised by this licence.

'NLRD' is a Notifiable low risk dealing. Dealings conducted as an NLRD must be assessed by an institutional biosafety committee (IBC) before commencement and must comply with the requirements of the Gene Technology Regulations 2001.

'OGTR' means the Office of the Gene Technology Regulator.

'Personal information' has the same meaning as in the *Privacy Act 1988*. Personal information means information or an opinion about an identified individual, or an individual who is reasonably identifiable:

- (a) whether the information or opinion is true or not; and
- (b) whether the information or opinion is recorded in a material form or not.

'Pharmacy' means a location within the clinical trial site, where authorised staff store, prepare, and dispense medications in a medical environment.

'Regulations' means the Gene Technology Regulations 2001 (Commonwealth) or the corresponding State law under which this licence is issued.

'Regulator' means the Gene Technology Regulator.

'Risk group 2 organism' means an organism that satisfies the criteria in AS/NZS 2243.3:2022 for classification as Risk Group 2.

'Sample' means any biological material collected from a treated trial participant for analysis as part of the trial.

Section 2 General conditions and obligations

Holder of licence

3. The licence holder is Doherty Clinical Trials Ltd (DCT).

Remaining an Accredited Organisation

4. The licence holder must, at all times, remain an accredited organisation.

Validity of licence

5. This licence remains in force until it is suspended, cancelled or surrendered. No dealings with the GMO are authorised during any period of suspension, or after the licence has been cancelled or surrendered.

Note: Although this licence has no expiry date, the duration of preparation and administration of the GMOs is restricted in accordance with Condition 25.

Persons covered by this licence

6. The persons covered by this licence are:
 - (a) the licence holder, and any employees, agents (or External service providers engaged by the licence holder); and
 - (b) the project supervisor(s); and
 - (c) other persons who are, or have been, engaged or otherwise authorised by the licence holder or the project supervisor to conduct any of the dealings authorised by this licence.
7. To the extent that any activity by a trial participant may be considered to be a dealing with the GMO as described in **Attachment A** for purposes of the Act, that dealing is authorised by this licence.
8. The licence holder must keep a record of all persons covered by this licence, and must keep a record of the contact details of the project supervisor(s) for the licence.

Note: Where External service providers are used, it is sufficient to record the company name and the position or job title of the person(s) conducting the dealing.

9. The licence holder must provide information related to the persons covered by the licence when requested to do so in writing by the Regulator and must provide the information within a time period stipulated by the Regulator.

Description of GMOs covered

10. The licence authorises specified dealings in respect of the GMOs identified and described in **Attachment A**.

Dealings authorised by this licence

11. The licence holder and persons covered by this licence may conduct the following dealings with the GMOs:
 - (a) conduct the following experiments with the GMOs:
 - i) prepare the GMO for administration;
 - ii) administer the GMO to clinical trial participants, one dose in each nostril by nasal spray;

- iii) collect Samples from trial participants;
- (b) transport the GMOs;
- (c) dispose of the GMOs;

and may possess, supply, use or store the GMO for the purposes of, or in the course of, any of these dealings.

12. Supply of the GMOs for the purposes of dealings by a person or organisation not covered by this licence is only authorised by this licence if the Regulator provides prior written approval to the licence holder.

Note: For approval to be granted, the receiving person or organisation must have an appropriate authorisation to conduct dealings with the GMOs. This is likely to be a NLRD or a licence issued by the Regulator.

13. This licence does not apply to dealings with the GMOs conducted as an NLRD or pursuant to another authorisation under the Act.

Conditions imposed by the Act

Note: The Act mandates the following 3 conditions.

Informing people of licence conditions (section 63)

14. The licence holder must inform any person covered by the licence, to whom a particular condition of the licence applies, of the following:
- (a) the particular condition, including any variations of it; and
 - (b) the cancellation or suspension of the licence; and
 - (c) the surrender of the licence.

Note: No particular conditions of this licence apply to trial participants; therefore, Condition 14 does not apply to trial participants.

Monitoring and audits (section 64)

15. If a person is authorised by this licence to deal with the GMOs and a particular condition of this licence applies to the dealing by that person, the person must allow the Regulator, or a person authorised by the Regulator, to enter premises where the dealing is being undertaken, for the purposes of auditing or monitoring the dealing.

Additional information to be given to the Regulator (section 65)

16. The licence holder must immediately inform the Regulator, if they become aware of:
- (a) additional information about any risks to the health and safety of people, or to the environment, associated with the dealings authorised by the licence; or
 - (b) any contraventions of the licence by a person covered by the licence; or
 - (c) any unintended effects of the dealings authorised by the licence.

Note 1: For the purposes of this condition:

- (a) *The licence holder is taken to have become aware of additional information if they were reckless as to whether such information existed; and*
- (b) *The licence holder is taken to have become aware of contraventions, or unintended effects, if they were reckless as to whether such contraventions had occurred, or such unintended effects existed.*

Note 2: Contraventions of the licence may occur through the action or inaction of a person.

Note 3: Additional information includes any changes, which might increase the likelihood of unintentional exposure of people or release of the GMO into the environment.

Note 4: An example of informing immediately is contact made at the time of the incident via the OGTR free call phone number 1800 181 030.

Informing the Regulator of any material changes of circumstance

17. The licence holder must immediately, by notice in writing, inform the Regulator of:

- (a) any relevant conviction of the licence holder occurring after the commencement of this licence;
- (b) any revocation or suspension after the commencement of this licence, of a licence or permit held by the licence holder under a law of the Commonwealth, a State or a foreign country, being a law relating to the health and safety of people or the environment;
- (c) any event or circumstances occurring after the commencement of this licence that would affect the capacity of the licence holder to meet the conditions in it.

18. The licence holder must provide information related to the licence holder's ongoing suitability to hold a licence when requested to do so in writing by the Regulator and must provide the information within a time period stipulated by the Regulator.

Further conditions with respect to informing persons covered by the licence

19. If a particular condition, including any variation of it, applies to an External service provider covered by this licence, the licence holder must not permit that person to conduct any dealings unless the person has been informed of the condition, including any variation of it.

Note: Information required under Condition 19 may be provided to External service providers who are engaged solely for transport of the GMO through labelling of the outermost container of the GMOs in accordance with Condition 39(a).

20. If a particular condition, including any variation of it, applies to a person with respect to any dealing, other than to an External service provider, the licence holder must not permit a person covered by this licence to conduct that dealing unless:

- (a) the licence holder has obtained from the person a signed and dated statement that the person:
 - i) has been informed by the licence holder of the condition and, when applicable, its variation; and
 - ii) has understood and agreed to be bound by the condition, or its variation; and
 - iii) has been trained in accordance with sub-condition 20(b) below; and

- (b) the licence holder has trained that person in a manner which enables them to conduct the dealings in accordance with the conditions of this licence.
21. The licence holder must notify all persons covered by the licence, from whom Personal information relevant to the administration and/or enforcement of the licence is collected by the licence holder, that such Personal information may be disclosed to the Regulator.
 22. The licence holder must ensure that a copy of the licence is readily available to all persons covered by the licence, other than External service providers, who are conducting dealings with the GMO.

Note: The licence may be made available electronically.

Section 3 Limits and control measures

Limits on clinical trials conducted under this licence

23. The clinical trials must be carried out at the in the Clinical trial site.
24. The GMO may be administered to a maximum of 150 trial participants.
25. The preparation and administration of the GMO must be completed within 5 years from the date of issuing of the licence.

Preparation and administration of the GMOs

26. Administration of the GMO to trial participants must not commence prior to approval by a Human Research Ethics Committee.

Conditions relating to Clinical trial site

27. The licence holder must ensure that administration of the GMOs is conducted within isolation rooms at the Clinical trial site.
28. The licence holder must ensure that during administration, isolation rooms are maintained at negative air pressure, relative to the adjacent common area.
29. The licence holder must ensure that each isolation room is equipped at all times with GMO-labelled waste bin, decontaminant, gloves, N95 masks, spill kits, and hand sanitiser.

Conditions relating to trial participants

30. The licence holder must notify each trial participant, from whom Personal information relevant to the administration and/or enforcement of the licence is collected by the licence holder, that such Personal information may be disclosed to the Regulator.
31. The licence holder must ensure that exclusion criteria used in selecting trial participants include (though are not limited to) Excluded persons as defined in this licence.
32. Before GMOs are administered to any trial participant, the licence holder must obtain written agreement from the trial participant that they will:
 - (a) remain at the Clinical trial site for at least 7 days after administration of the GMO; and
 - (b) agree to take antiviral medication if they are shedding the GM virus at day 6 after administration of the GMO, as confirmed by tests conducted on nasal specimen; and

- (c) agree to isolate at home and avoid contact with people at higher risk for influenza-related complications, including Persons ≥ 65 years of age or < 5 years of age, or pregnant or breastfeeding person if tested positive for the GMO 7 days after administration of the GMO.
33. The licence holder must inform the trial participant of the potential consequences resulting from exposure to the GMO by vulnerable people as a result of withdrawing from the clinical trial.

Conditions related to the conduct of the dealings

34. Conditions that apply to dealings with GMOs do not apply to Samples collected from trial participants, or other materials or waste, that are reasonably expected not to contain the GMO. The licence holder must provide to the Regulator upon request, a written justification for this expectation.
35. The licence holder must ensure that dealings are only conducted in a manner which:
- (a) does not compromise the health and safety of people; and
 - (b) minimises the exposure of persons conducting the dealings to the GMO, other than intended exposure of trial participants.

Note: The licence holder may achieve this by only engaging or otherwise authorising persons to conduct dealings who are required to adhere to appropriate standards and guidelines. For example, standards developed by the National Pathology Accreditation Advisory Council for pathology practices, the Australian Guidelines for the Prevention and Control of Infection in Healthcare, Guidelines for Good Clinical Practice and the National Safety and Quality Health Service (NSQHS) Standards, or the behavioural requirements for dealings conducted in OGTR certified facilities.

36. The licence holder must ensure that procedures are in place to account for the GMO from receipt of the GMO at the Clinical trial site to destruction, and records must be made available to the Regulator on request.
37. The licence holder must ensure that DCT staff conducting dealings:
- (a) have been informed of the risks associated with exposure to the GMOs for persons ≥ 65 years of age or < 5 years of age, or pregnant or breastfeeding persons;
 - (b) have a current seasonal influenza vaccination.

Work practices at Clinical trial site

38. For the purposes of Condition 35, work practices and behaviours within the Clinical trial site must include, but are not limited to, the following:
- (a) all DCT staff entering the isolation room must wear appropriate PPE including fitted N95 mask, gown, goggles, gloves, closed shoes, and shoe coverings;
 - (b) during the clinical trial, access to the isolation rooms must be restricted to authorised personnel only;
 - (c) participants must wear surgical masks for an additional 1.5 hours after administration of the GMOs to limit the spread of droplets and aerosols;

- (d) Prior to exiting the isolation room, all PPE must be removed except for the N95 facemask, the door handle surface-Decontaminated and hands must be Decontaminated. The facemask must be removed in the hallway once the isolation room door is closed;
- (e) all disposable PPE must be disposed of in GMO-labelled bins;
- (f) all work surfaces within the isolation room must be decontaminated after administration of the GMO;
- (g) equipment used for dealings with the GMOs and reusable PPE must be Decontaminated after use;
- (h) preparation and administration of the GMO must be conducted by suitably qualified and trained staff;
- (i) following the departure of the trial participant from the isolation room, all bedding and potentially contaminated surfaces must be Decontaminated.

Transport, storage and disposal of the GMOs

39. The licence holder must ensure that transport and storage of the GMOs within the Clinical trial site follows these sub-conditions:

- (a) GMOs must be contained within a sealed, unbreakable primary and secondary container(s), with the outer packaging labelled to indicate at least:
 - i) that it contains GMOs; and
 - ii) that it contains biohazardous material as designated by a biohazard label; and
- (b) the external surface of the primary and secondary container must be Decontaminated prior to transport; and
- (c) access to the GMOs is restricted to authorised persons for whom Condition 19 or Condition 20 has been met (i.e. the GMOs are within a locked unit or an area which has restricted access). This includes situations where containers are left for collection in a holding area, or left unattended prior to Decontamination; and

Note: All stored GMOs remain the responsibility of the licence holder.

- (d) if the GMO is being transported or stored with a coolant (e.g. dry ice, liquid nitrogen or any other coolant) which will release a gas, a mechanism to allow the escape of the gas must be included. If water ice is used as a coolant then the outer packaging should be constructed so as to prevent any leakage. All containers must be able to withstand the temperatures to which they will be subjected; and

Note: When transporting and storing with coolants, it is preferable for coolants to be used outside of the secondary container.

- (e) a consolidated record of all GMOs being stored under this condition is maintained and made available to the Regulator upon request.

40. The licence holder must ensure that all GMOs and waste reasonably expected to contain the GMOs are Decontaminated:

- (a) prior to disposal, unless the method of disposal is also a method of Decontamination; and
- (b) before or upon suspension, cancellation or surrender of the licence, unless covered by another authorisation under the Act, or exported; and
- (c) by autoclaving, chemical treatment, high-temperature incineration or any other method approved in writing by the Regulator.

41. Where transport is conducted by External service providers for the purpose of destruction, the licence holder must ensure that the GMO, or waste reasonably expected to contain the GMO, is disposed in bin labelled as containing GMOs and Decontaminated via autoclaving or high-temperature incineration.

Note: In the event of a spill during transport by an External service provider, compliance with relevant State or Territory legislation and regulations to manage clinical or biohazardous spills is sufficient.

Contingency plans

42. The licence holder must ensure that any person (other than a trial participant) exposed to the GMOs is offered prompt medical attention. The clinician must be provided with any relevant information about the GMO, including any drugs to which it may be effective or resistant.
43. In the event of an exposure to the GMOs and a person authorised under this licence displays influenza symptoms, the licence holder must ensure:
- (a) the person is tested for the GMO currently used in the facility; and
 - (b) if the GMO is detected, the person must isolate and be treated with antivirals.
44. If there is a spill or an unintentional release of the GMOs at the Clinical trial site or during transport, the following measures must be implemented:
- (a) the GMOs must be contained to prevent further dispersal; and
 - (b) persons cleaning up the GMO must wear appropriate PPE including N95 mask, gown, goggles, gloves, closed shoes, and shoe coverings; and
 - (c) the exposed area must be Decontaminated with an appropriate chemical disinfectant effective against the GMOs, such as 80%v/v ethanol; and
 - (d) any material used to clean up the spill or PPE worn during clean-up of the spill must be Decontaminated; and
 - (e) the licence holder must be notified as soon as reasonably practicable.

Section 4 Reporting and Documentation

*Note: The following licence conditions are imposed to demonstrate compliance with other conditions and facilitate monitoring of compliance by staff of the OGTR. Notices and reports may be emailed to OGTR.M&C@health.gov.au. A summary of notification and reporting requirements is provided at **Attachment B**.*

45. At least 14 days prior to first administering each GMO variant, or a timeframe agreed to in writing by the Regulator, the licence holder must provide the Regulator with a Compliance Management Plan, specifying:

- (a) the role and contact details for key persons responsible for the management of the trial;
- (b) the proposed reporting structure for the trial at the site and how the reporting structure enables the licence holder to become aware of all reportable events including but not limited to Conditions 15, 16, 44 and 47;
- (c) the details of the GMO, including but not limited to the name of the variant;
- (d) the number of trial participants enrolled;
- (e) the type of studies conducted in association with the GMO (test of a vaccine, an antiviral drug or infectivity study);
- (f) how compliance with Condition 35 will be achieved in relation to preparation of participant Samples for analysis subsequent to administering the GMO;
- (g) the expected date of first administration.

Note: For the purpose of finding out whether the Act has been complied with, an OGTR inspector may, if entry is at a reasonable time, enter a facility occupied by the licence holder or a person covered by the licence and exercise monitoring powers.

46. The licence holder must notify the Regulator, in writing, no later than 30 days after:

- (a) the final dose being administered; or
- (b) the decision that no further trial participants will be treated at that site.

47. The licence holder must inform the Regulator as soon as reasonably possible:

- (a) in the event of a loss or spill of the GMO;
- (b) in the event of the exposure of a person other than a trial participant, to the GMO; and
- (c) if a trial participant has not followed the procedures described in the instructions provided by the licence holder.

48. Upon request from the Regulator, the licence holder must provide any signed records or documentation collected under a condition of this licence, within a time period stipulated by the Regulator.

Attachment A**DIR No: 210****Title:** Clinical trials of controlled infection with seasonal Influenza viruses**Organisation Details** Doherty Clinical Trials Ltd (DCT)

Postal address: 2 St Andrews Place

East Melbourne

Victoria, 3002

Phone No: (03) 9970 4200

GMO Description**GMOs covered by this licence:**

Recombinant influenza virus A and B as listed in Table 1

Parent Organisms:**Common Name:** Influenza Virus**Scientific Name:** Influenza Virus A and B (Orthomyxoviridae family)**Modified traits:**

Categories: Human therapeutic

Description: The GMOs are influenza viruses (A and B) produced through reverse genetics and are similar to naturally circulating influenza viruses as described in Table 1.

Table 1. Nucleic acid responsible for conferring the modified traits

Genetic modifications	
Source, identity, nature of modification	Modified trait description
Rescue of infectious influenza viruses (GMO) from cloned cDNA. The GMOs are genetically similar to the seasonal influenza virus, which is the parent organism. No deliberate changes are made to the genetic material in the GMOs.	

Trial participants and route of administration of the GMOs

In this clinical trial, healthy participants will receive a single dose of the GMOs intranasally using an atomiser fitted with a syringe.

Attachment B – Summary of reporting requirements*

Prior to the commencement of the trial	Condition	Timeframe for reporting
<p>A written Compliance Management Plan for clinical trial site:</p> <ul style="list-style-type: none"> (a) the role and contact details for key persons responsible for the management of the trial; (a) the proposed reporting structure for the trial at the site and how the reporting structure enables the licence holder to become aware of all reportable events including but not limited to Conditions 15, 16, 44 and 47; (b) the details of the GMO, including but not limited to the name of the variant; (c) the number of trial participants enrolled; (d) the type of studies conducted in association with the GMO (test of a vaccine, an antiviral drug or infectivity study); (e) how compliance with Condition 35 will be achieved in relation to preparation of participant Samples for analysis subsequent to administering the GMO. (f) the expected date of first administration. 	45	At least 14 days prior to the first administration of the GMO at clinical trial site, or a timeframe agreed to in writing by the Regulator
Information to be provided at any time during the clinical trial	Condition	
Any additional information related to the health and safety of people and the environment associated with the dealings covered by the licence, or any unintended effects of the dealings authorised by the licence	16(a), (c)	Immediately
Information related to any contravention of the licence by a person covered by the licence	16(b)	Immediately
Any relevant conviction of the licence holder	17(a)	Immediately
Any revocation or suspension of a licence or permit held by the licence holder under a law of the Commonwealth, a State or a foreign country	17(b)	Immediately
Any event or circumstances that would impact the licence holder capacity to meet the licence conditions	17(c)	Immediately
Provide notification to the Regulator, in writing, of the final GMO administration of the last trial participant at each clinical trial site	46(a)	Within 30 days of the decision to cease GMO administration at clinical trial facility

Any Serious adverse event which may be related to the GMO	47(a)	Any Serious adverse event which may be related to the GMO
Any loss or spill of the GMO, or exposure of a person other than the trial participant to the GMO	47(b), (c)	As soon as reasonably possible
Any event where a trial participant has not followed the procedures described in the instruction provided by the licence holder	47(d)	As soon as reasonably possible
Information to be provided on request by the Regulator		
Information related to the persons covered by the licence	9	Within a timeframe stipulated by the Regulator
Information related to the licence holder's ongoing suitability to hold a licence	18	Within a timeframe stipulated by the Regulator
Copies of signed and dated statements and training records	20	Within a timeframe stipulated by the Regulator
Any signed records or documentation collected under a condition of this licence	48	Within a timeframe stipulated by the Regulator

* Notifications and documents to be sent to OGTR.M&C@health.gov.au

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