



Australian Government

Department of Health

Office of the Gene Technology Regulator

Risk Assessment and Risk Management Plan for

DIR 144

Clinical trial of live attenuated genetically modified
influenza vaccines

Applicant: Clinical Network Services (CNS) Pty Ltd

July 2016

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Summary of the Risk Assessment and Risk Management Plan

for

Licence Application No. DIR 144

Decision

The Gene Technology Regulator (the Regulator) has decided to issue a licence for this application to conduct dealings with genetically modified (GM) influenza (flu) vaccines. A Risk Assessment and Risk Management Plan (RARMP) for this application was prepared by the Regulator in accordance with the requirements of the *Gene Technology Act 2000* (the Act) and corresponding state and territory legislation, and finalised following consultation with a range of experts, agencies and authorities, and the public. The RARMP concludes that this clinical trial poses negligible to low risks to human health and safety and the environment, and that risks posed by the dealings can be managed by imposing conditions on the conduct of the trial.

As part of Australia's integrated approach to the regulation of gene technology, regulation under the Act is not intended to override or duplicate the regulatory oversight of agencies that have responsibility for genetically modified organisms (GMOs) or GM products based on their intended use.

Clinical trials in Australia must be conducted in accordance with requirements of the *Therapeutic Goods Act 1989*, which is administered by the Therapeutic Goods Administration (TGA). Clinical trials of therapeutic products that are experimental and under development are regulated by the TGA through the Clinical Trial Exemption (CTX) scheme or the Clinical Trial Notification (CTN) scheme. CNS has indicated that they will submit a Clinical Trial Notification to the TGA. Clinical trials are also required to have approval from the Human Research Ethics Committee (HREC) at each trial site before the trial commences, and must be conducted in accordance with the National Statement on the Ethical Conduct in Research Involving Humans.

The application

Application number	DIR 144
Applicant	Clinical Network Services (CNS) Pty Ltd
Project title	Clinical trial of live attenuated genetically modified influenza vaccines ¹
Parent organism	Human influenza A virus and influenza B virus
Genetic modification and novel traits	GMO type 1 (CodaVax and other Synthetic Attenuated Virus Engineering (SAVE) flu vaccines): Modified haemagglutinin (HA) and neuraminidase (NA) genome segments, for influenza virus attenuation GMO type 2 (FluMist): Substituted HA and NA genome segments, for antigen expression
Proposed release dates	The clinical trial would commence when all the required approvals have been granted
Proposed duration	5 years

¹The title of the licence application as submitted by CNS 'Limited and controlled released of a live-attenuated seasonal influenza vaccine CodaVax and other influenza vaccines manufactured using the SAVE technology vaccine platform in addition to the quadrivalent live attenuated influenza vaccine (FluMist®)'

Proposed location	For administration in clinical facilities experienced in conducting clinical trials. One trial site in Brisbane, Queensland has been proposed for the initial trial. Additional trial sites in Melbourne, Perth and Adelaide may be included for later trials.
Primary purpose	To assess the safety and tolerability of CodaVax and other SAVE flu vaccines, with FluMist flu vaccines as a comparator.

CNS proposed to conduct clinical trials of GM flu vaccines. This clinical study would assess the safety and tolerability of a new type of live attenuated influenza vaccine (LAIV), known as Synthetic Attenuated Virus Engineering (SAVE) flu vaccines. The study would compare the GM SAVE flu vaccines to another GM live flu vaccine, FluMist. FluMist is commercially available in the United States of America (USA), Canada and the European Union (EU). FluMist has also been issued a licence by the Regulator for commercial supply in Australia, and is awaiting approval from the TGA for use as a human therapeutic.

The SAVE and FluMist vaccines would be administered by qualified health professionals in clinical facilities. To date only one site in Queensland has been confirmed for the clinical trial but other sites may be engaged.

The proposed initial trial would use a single Influenza A vaccine strain genetically modified according to the SAVE design strategy, known as CodaVax. This initial trial will involve up to a total of 100 patients, and will be conducted in Queensland. Later trials are proposed to involve multiple SAVE flu vaccine strains (e.g. trivalent or quadrivalent SAVE flu vaccines containing up to two GM Influenza A strains and two GM Influenza B strains developed using the SAVE design strategy). The GM flu vaccines would be nasally administered to up to a maximum of 500 trial participants at designated clinical facilities over a 5 year period. Blood and urine samples would be collected from trial participants and either analysed in laboratories within Australia or exported for testing overseas.

The GM flu vaccines would be manufactured in the USA and imported into Australia.

Risk assessment

The risk assessment concludes that risks from the proposed dealings to the health and safety of people, or to the environment, are negligible to low. It is proposed that risk treatment measures be applied to manage these risks.

The risk assessment process considers how the genetic modification and proposed activities conducted with the GMOs could lead to harm to people or the environment. Plausible causal or exposure pathways are postulated that may give rise to harm for people or the environment from dealings with a GMO (risk scenarios) in the short and long term. This included consideration of the presence of the parent organism in the Australian environment and the potential for: the genetic modifications to impact on the characteristics of the GM flu viruses; infection of people, including at-risk individuals; and infection of animals. The opportunity for gene transfer to other organisms, and its effects if it were to occur, was also considered.

A risk is only identified for further assessment when a risk scenario is considered to have some chance of causing harm. Pathways that do not lead to an adverse outcome, or could not reasonably occur, do not advance in the risk assessment process. Identified risks are characterised in relation to both the likelihood and seriousness of harm, taking into account information in the application (including proposed limits and controls), relevant previous approvals and current scientific/technical knowledge.

The TGA, the trial sponsor, the investigators and the Human Research Ethics Committee (HREC) at each trial site all have roles to play in ensuring participants' safety under the

Therapeutic Goods Act 1989. Therefore, the Regulator focuses primarily on risks posed to people other than those participating in the clinical trial, and to the environment.

Exposure of at-risk individuals through contact with trial participants who are shedding CodaVax or FluMist vaccine strains was estimated as posing negligible to low risks to human health and safety. Other, as yet unspecified SAVE flu vaccines were estimated as posing negligible to low risks to health and safety of people and animals. Risk evaluation proposed that risk treatment should be applied to mitigate the low risks. No other substantive risks were identified.

Important factors in reaching the conclusions of the risk assessment included: that the GM flu vaccines are expected to be attenuated relative to unmodified flu virus; unintended exposure would be minimised by precautions proposed by the applicant; and previous experience with the FluMist vaccines in other jurisdictions.

As risks to the health and safety of people, or the environment, from the proposed clinical trials of the GM flu vaccines have been assessed as negligible to low, the Regulator considers that the dealings involved do not pose a significant risk to either people or the environment.

Risk management plan

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 evaluates options for treatment of identified risks, evaluates limits and controls proposed by the applicant, and considers general risk management measures. The risk management plan is given effect through licence conditions.

Treatment measures to mitigate the identified negligible to low risks to human health and safety were considered, and licence conditions imposed. These conditions require patients participating in the trial to avoid contact with certain at-risk people following inoculation with the GMO, and the licence holder must provide details of genetic modifications and evidence for the attenuation of each individual SAVE flu vaccine strain before it is included in the trials. These measures are considered sufficient to manage the identified negligible to low risks.

As this is a limited and controlled release, the licence also includes conditions that limit the scope and duration of the trial as well as controls in line with those proposed by the applicant, including:

- administration of the GM flu vaccines, at suitable clinical facilities, via nasal inoculation by trained medical staff
- exclusion of participants/clinical staff at higher risk of adverse reactions
- educating trial participants about methods to minimise transmission of the GMO's, including the disposal of GMO contaminated waste
- appropriate containment and waste disposal provisions at the clinical site
- destroying excess GMO that is not required for further studies
- transporting and storing the GMO in accordance with the *Regulator's Guidelines for the Transport, Storage and Disposal of GMOs* or relevant international transport guidelines.

The licence also contains a number of general conditions relating to ongoing licence holder suitability, auditing and monitoring, and reporting requirements, which include an obligation to report any unintended effects.

These licence conditions will manage risks to so as to protect human health and safety and the environment.

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Abbreviations

ACIP	Advisory Committee on Immunization Practices
AIVC	Australian Influenza Vaccine Committee
BSC	biological safety cabinet
CCI	Confidential Commercial Information under section 185 of the <i>Gene Technology Act 2000</i>
CDC	Center for Disease Control and Prevention
CNS	Clinical Network Services (CNS) Pty Ltd
CPD	codon pair deoptimisation
CRO	Clinical research organisation
CTN	Clinical Trial Notification
CTX	Clinical Trial Exemption
DIR	Dealings involving Intentional Release
DNA	Deoxyribonucleic acid
EU	European Union
flu	influenza
GM	Genetically modified
GMO	Genetically modified organism
HA	haemagglutinin
HREC	Human Research Ethics Committee
IATA	International Air Transport Association
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
HGT	Horizontal gene transfer
IC ₅₀	half maximal inhibitory concentration
LAIV	live attenuated influenza vaccine
MDCK	Madin-Darby Canine Kidney
mL	millilitre
NA	neuraminidase
NHMRC	National Health and Medical Research Council
OGTR	Office of the Gene Technology Regulator
pfu	plaque-forming units
PPE	Personal Protective Equipment
RARMP	Risk Assessment and Risk Management Plan
SAVE	Synthetic Attenuated Virus Engineering
TGA	Therapeutic Goods Administration
the Act	<i>The Gene Technology Act 2000</i>
the Regulations	The Gene Technology Regulations 2001, as amended 2011
the Regulator	The Gene Technology Regulator
US CDC	United States Center for Disease Control and Prevention
USA	United States of America
WHO	World Health Organization

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 in conjunction with the Gene Technology Regulations 2001 (the Regulations), an inter-governmental agreement and corresponding legislation that is being enacted in each State and Territory, 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. This chapter describes the parameters within which potential risks to the health and safety of people or the environment posed by the proposed release are assessed. The risk assessment context is established within the regulatory framework and considers application-specific parameters (Figure 1).

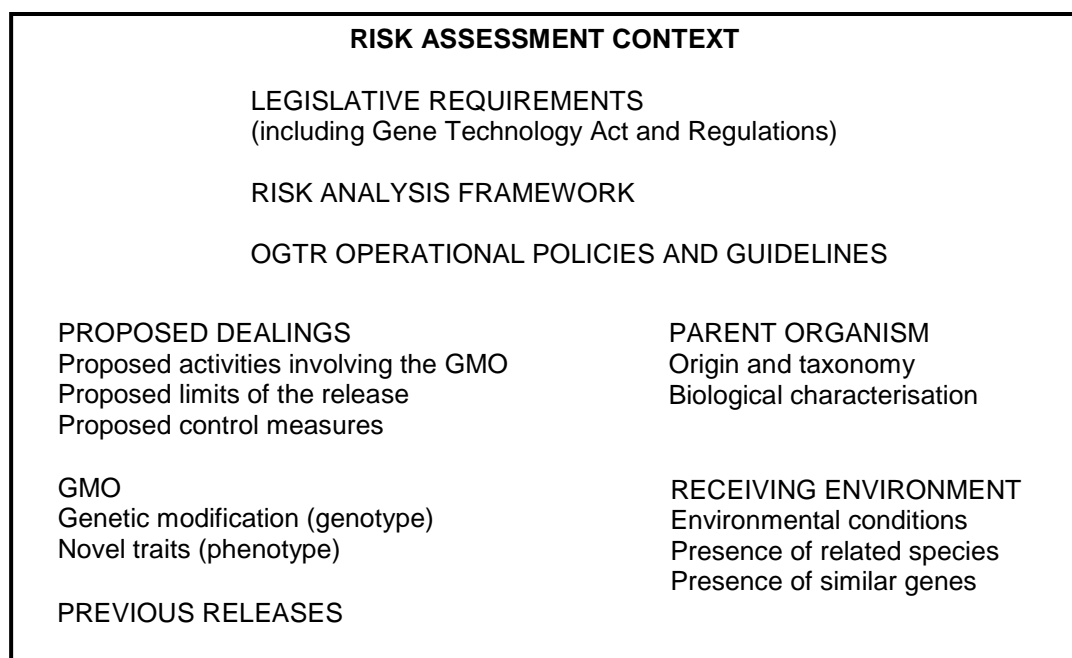


Figure 1. Summary of parameters used to establish the risk assessment context

Section 2 Regulatory framework

4. Sections 50, 50A and 51 of the Act outline the matters which the Gene Technology Regulator (the Regulator) must take into account, and consultation that is required when preparing the Risk Assessment and Risk Management Plans (RARMPs) that inform decisions on licence applications. In addition, the Regulations outline matters the Regulator must consider when preparing a RARMP.
5. In accordance with section 50A of the Act, this application is considered to be a limited and controlled release application, as its principal purpose is to enable the applicant to conduct experiments and the applicant has proposed limits on the size, locations and duration of the release, as well as controls to restrict the spread and persistence of the GMOs and their genetic material in the environment. Therefore, the Regulator was not required to consult with prescribed experts, agencies and authorities before preparation of the RARMP (see section 50 of the Act).

6. Section 51 of the Act and regulation 9A of the Regulations outline the matters the Regulator must take into account in preparing a RARMP.

7. Section 52 of the Act requires the Regulator to seek comment on the RARMP from the States and Territories, the Gene Technology Technical Advisory Committee, Commonwealth authorities or agencies prescribed in the Regulations, the Minister for the Environment, relevant local council(s), and the public. Advice from the prescribed experts, agencies and authorities, and how it was taken into account, is summarised in Appendix A. One submission was received from a member of the public, summarised in Appendix B.

8. The Risk Analysis Framework explains the Regulator's approach to the preparation of RARMPs in accordance with the legislative requirements (OGTR 2013). Additionally, there are a number of operational policies and guidelines developed by the Office of the Gene Technology Regulator (OGTR) that are relevant to DIR licences. These documents are available from the [OGTR website](#).

2.1 Interface with other regulatory schemes

9. Gene technology legislation operates in conjunction with other regulatory schemes in Australia. Any 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 National Industrial Chemicals Notification and Assessment Scheme and the Department of Agriculture. These dealings may also be subject to the operation of State legislation declaring areas to be GM, GM free, or both, for marketing purposes.

10. 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 Exemption (CTX) scheme or the Clinical Trial Notification (CTN) scheme.

11. For clinical trials, the TGA has regulatory responsibility for the supply of unapproved therapeutic products. In terms of risk to individuals participating in a clinical trial, the TGA (as the primary regulatory agency), the trial sponsor, the investigators and the Human Research Ethics Committee (HREC) at each trial site all have roles in ensuring participants' safety under the *Therapeutic Goods (Therapeutic Goods Administration 2000) Act 1989*. 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 GM virus, and risks associated with import, transport and disposal of the GMO.

12. The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – *Guidelines for Good Clinical Practice* (ICH-GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects (ICH 1996). The guideline was developed with consideration of the current good clinical practices of the European Union (EU), Japan, and the United States of America (USA), as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO). The TGA has adopted the ICH-GCP in principle as *Note for Guidance on Good Clinical Practice* (designated

CPMP/ICH/135/95) (Therapeutic Goods Administration 2000), which provides overarching guidance for conducting clinical trials in Australia which fall under TGA regulation.

13. The National Health and Medical Research Council (NHMRC) has issued the *National Statement on the Ethical Conduct in Research Involving Humans* (National Health and Medical Research Council 2013). This document sets the Australian standard against which all research involving humans is reviewed. The *Therapeutic Goods Act 1989* requires that the use of a therapeutic good in a clinical trial must be in accordance with the ethical standards set out in this document.

14. Approval by a HREC is also a fundamental requirement of a clinical trial. HRECs conduct both ethical and scientific assessment of the proposal and in addition often consider issues of research governance. Other elements of governance of clinical trials that are considered by HRECs include appropriate informed consent, specific inclusion and exclusion criteria, data monitoring and vaccine accounting and reconciliation.

15. The Department of Agriculture administers Australian biosecurity conditions for the importation of biological products under the *Quarantine Act 1908*. Biological products include animal or microbial derived products such as foods, therapeutics, laboratory materials and vaccines (including GM vaccines). Import of GM virus is subject to regulation by the Department of Agriculture and the Regulator.

Section 3 Dealings proposed by the applicant

16. This section describes the GMO dealings, the limits and the controls that the applicant has proposed. These dealings, limits and controls are considered in the risk assessment (Chapter 2). Risk management (Chapter 3) then evaluates the suitability of proposed limits and controls, as well as other risk management measures that may be appropriate. As a result, licence conditions may differ from what is proposed by the applicant.

17. CNS proposes to conduct clinical trials with a new type of GM live attenuated influenza vaccine (LAIIV) developed using the Synthetic Attenuated Virus Engineering (SAVE) design strategy, referred to as SAVE flu vaccines. The initial SAVE flu vaccine strain for the clinical trials is known as CodaVax. The trials would assess the safety and tolerability of CodaVax or other SAVE flu vaccines, using FluMist flu vaccine as a comparator. The CodaVax, other SAVE flu vaccines and FluMist vaccines would be manufactured in the USA and imported into Australia. The GM flu vaccines would be administered intranasally to healthy adult male volunteers, and samples that may contain GMOs would be collected from trial participants for analysis in laboratories within Australia or exported for testing overseas.

3.1 The proposed clinical trials

3.1.1 Conduct of the clinical trials

18. The proposed clinical studies involve three arms: experimental group (receiving the GM CodaVax or other SAVE flu vaccine), active comparator group (receiving FluMist vaccine) and placebo group.

19. The international trial sponsor is Codagenix Inc., based in the USA. Codagenix has contracted Clinical Network Services (CNS) Pty Ltd to manage regulatory compliance for the Australian component of the trials.

20. The initial SAVE flu vaccine strain for the clinical trials, CodaVax, is based on the pandemic A/California/07/2009 (H1N1) flu strain. This flu strain has been the basis for the H1N1 vaccine component of the seasonal influenza vaccine for the past three seasons. This initial trial will involve up to a total of 100 patients, and will be conducted in Queensland.

21. The selection of target flu strains for development of additional as of yet unspecified SAVE flu vaccines for inclusion in the study will depend on World Health Organization

(WHO) and Australian Influenza Vaccine Committee (AIVC) advice on the antigen composition of flu vaccines for the current or upcoming flu season for the southern hemisphere.

22. The trials will be divided into four stages:

- 1) Screening: medical history and health status of prospective volunteers will be examined and their suitability to participate in the study assessed.
- 2) Treatment: trial participants will undergo a single treatment with either SAVE flu vaccine, FluMist flu vaccine or placebo. SAVE flu vaccines will be nasally administered to trial participants as a 0.2 mL unit dose (approximately 0.1 mL per nostril) containing 5×10^4 plaque-forming units (pfu)/mL. CodaVax will be delivered using a dropper in the first clinical trial, while either a dropper or sprayer (similar to FluMist) may be used for other SAVE flu vaccines in subsequent trials. FluMist will contain 10^7 pfu/mL administered as a 0.2 mL unit dose (approximately 0.1 mL per nostril) as an aerosol using the sprayer in which it is commercially supplied.
- 3) Monitoring: All Groups will be monitored daily at the clinical site from days 1 to 6 post-vaccination, at which time their symptoms will be assessed and their blood pressure, temperature and heart rate recorded. Blood and urine samples will be taken for testing for the presence of Influenza A virus. Participants will be instructed to report any adverse events (fever $>100^\circ\text{F}$ [37.8°C]; runny nose; nasal congestion; sore throat; headache; malaise; muscle ache; chills; decreased appetite; vomiting) during their scheduled visits to the clinical site.
- 4) Final follow-up: Between days 30 to 35, trial participants will return for a final follow-up visit to the clinical site. Blood will be taken for measurement of anti-A/California/07/2009 (H1N1) antibodies, or antibodies to the appropriate flu strain, in their serum via a hemagglutination inhibition assay (HAI).

23. Clinical staff conducting the dealings, including the principal investigator, sub-investigator, study coordinator, clinical site nursing staff and pharmacists, will be trained in product handling at a site-initiation visit by a medical monitor who themselves will have been trained in the conditions of the licence. CNS will audit trial sites periodically and ensure compliance with regulatory requirements.

24. Under the *Gene Technology Act 2000*, the proposed clinical trials involve the following dealings:

- a) importing the GMOs;
- b) conducting experiments with the GMOs;
- c) transporting the GMOs;
- d) disposing of the GMOs; and
- e) possession (including storage) and use of the GMOs for the purpose of any of the above activities.

3.1.2 Selection of trial participants

25. The inclusion and exclusion criteria for trial participants will be appropriate to ensure the safety of the individuals involved in the trial and approved by a HREC.

26. Inclusion criteria to be used by study site investigators include:

- a) healthy adult males.

27. Exclusion criteria include:

- a) persons with a known immune deficiency, including Human Immunodeficiency Virus (HIV);
- b) persons with pet birds;
- c) persons with a known hypersensitivity to any of the components in the SAVE flu vaccines;
- d) persons with hypersensitivity to the active substances or to any of the excipients in FluMist (e.g. gelatin), or to gentamicin (a possible trace residue), to eggs or to egg proteins (e.g. ovalbumin); and
- e) persons unable or unwilling to comply with the requirements of the trial protocol.

3.1.3 Instructions to trial participants

28. Trial participants treated with the GMO will receive instructions intended to minimise interpersonal spread of the GM virus – in particular, to individuals at risk of developing severe disease. The applicant has confirmed that these behaviours will be a required part of the clinical trials protocol, and unwillingness or inability to comply is grounds for exclusion from the trial (see paragraph 27 (e)).

29. Relevant information for participants will be provided in the Informed Consent Form (ICF) and explained by a member of the clinical site medical staff before treatment. The ICF will indicate to the participant that they may be receiving a genetically modified vaccine and that they should not donate blood, tissues or organs while participating in the trials.

30. Trial participants will also be instructed to use tissues to collect any respiratory secretions as a result of sneezing, coughing or eye secretions for seven days after treatment, to be returned to the clinical sites for appropriate disposal (as detailed later in this section).

3.1.4 Transport and storage of the GMO

31. The GMO's will be manufactured according to Good Manufacturing Practice guidelines in the USA and imported into Australia. Concentrated CodaVax and other SAVE flu vaccines will be supplied in small volumes in sealed vials, and FluMist will be imported in pre-packaged nasal sprayers, labelled to indicate the contents, quantity and clinical trial details according to TGA requirements for human therapeutics.

32. Contractors will be responsible for transporting the GM flu vaccines from the point of import directly to the clinical research organisation (CRO)/Study Site. For transport during import and distribution to the clinical facilities within Australia, all the GM flu vaccines will be packaged to meet the requirements of International Air Transport Association (IATA) shipping classification Biological Substance UN 3373, Category B.

33. During transport, primary containers will be shipped in sealed plastic bags. Secondary boxes/cartons will be labelled to indicate that they contain GMO's. CodaVax and other SAVE flu vaccines will be shipped from the USA to Australia at a temperature of $-20^{\circ}\text{C} \pm 10^{\circ}\text{C}$; FluMist vaccines will be shipped at a temperature of $+2$ to $+8^{\circ}\text{C}$.

34. Once at the pharmacy or final destination, all the GM flu vaccines will be stored in a secure location with access limited to the site pharmacist and medical staff according to the *National vaccine storage guidelines: Strive for 5, 2nd Edition* (Department of Health and Ageing 2013) and the *Standard for the Uniform Scheduling of Medicines and Poisons* (Therapeutic Goods Administration 2016).

35. Blood and urine samples will be collected from trial participants during the study. Testing of the samples will be performed at a pathology testing facility associated with the

clinical trial unit or may be exported for analysis overseas. These samples may contain the GMOs, and will be double contained during transport.

3.1.5 Handling of the GMO

Procedures

36. Written authorisation from the principal investigator will be required before any GM flu vaccine is dispensed by pharmacy or laboratory staff designated and trained for this study. The GM flu vaccines will be double contained during transport within clinical facilities.

37. Concentrated CodaVax and other SAVE flu vaccines will be drawn into a syringe and diluted in either saline or sucrose phosphate buffer in a biosafety cabinet and loaded into nasal droppers (or possibly sprayer for later trials) at the trial site. FluMist vaccine will be sent to the pharmacist in its original packaging and administered via the sprayer as described in the package insert.

38. The administration of the GM flu vaccines will be under the responsibility of the investigator, according to the clinical protocol and in accordance with ICH-GCP (ICH 1996) and TGA Good Clinical Practice guidelines (Therapeutic Goods Administration 2000).

Safety considerations

39. All clinical trial staff will have an influenza vaccination one month prior to handling the vaccines. There will be no exclusion criteria applied to vaccinated staff handling the GM flu vaccines.

40. When handling the GM flu vaccines, personal protective equipment (PPE) are to be used (e.g. gloves, gown, etc., as appropriate based on risk assessment). In addition, relevant institutional policies and procedures should be followed.

41. Dilution of concentrated CodaVax and other SAVE flu vaccines will be done in a biological safety cabinet (BSC).

42. Administration of the GMO and subsequent care of inoculated participants will be, at a minimum, in accordance with the Australian Guidelines for the Prevention and Control of Infection in Healthcare (National Health and Medical Research Council 2010). These guidelines aim to reduce transmission of infectious organisms from both recognized and unrecognized sources in the clinical setting. Appropriate practices include (but are not limited to) hand hygiene, use of PPE as appropriate and based on risk assessment, safe sharps handling and disposal practices, safe handling of potentially contaminated equipment or surfaces in the patient environment, respiratory hygiene/cough etiquette and correct cleaning and waste management.

3.1.6 Disposal of the GMOs (including waste contaminated with the GMOs)

43. Following acquittal of all investigational products by the CRO responsible for the site(s), used vials, droppers or sprayers will be placed into medical waste containers following the sites' procedures for the disposal of biohazardous material. Other secondary waste generated during the vaccination procedure (i.e. gloves, syringes and alcohol swabs etc.), and any unused GM flu vaccines, will be discarded into appropriate biohazard containers and disposed of following the sites' procedures for the disposal of biohazardous material in accordance with the requirements of the *Work Health and Safety Act 2011 (C'wth)* and related state and territory legislation.

44. After handling the GM flu vaccines, work surfaces will be decontaminated with an appropriate chemical disinfectant, following standard institutional procedures. Contaminated textiles (e.g. linens, towels and clothing) will be laundered using routine protocols for healthcare facilities (e.g. hot (71°C) water with detergent and hot air drying).

45. Trial participants will be instructed to use tissues to collect any respiratory secretions as a result of sneezing, coughing or eye secretions for seven days after administration. Participants will be instructed to place all tissues used to collect any respiratory secretions into small sealable bags, which in turn are to be placed within biohazard containers provided by the applicant at the time of administration. Following placement of the tissues into the biohazard container, participants will be instructed to wash their hands with soap and water. The biohazard containers with the bags of used tissues are to be returned to the clinical site for standard disposal of biohazard material by the institution.

3.1.7 Contingency plans

46. In the event of accidental spill of the GM flu vaccines, the applicant has proposed the following:

- a) select and wear appropriate PPE
- b) contain spill immediately with absorbent material
- c) place contaminated absorbent material into impervious container or plastic bag for disposal
- d) clean the area with warm detergent solution
- e) wipe the area with sodium hypochlorite or appropriate disinfectant, and
- f) perform hand hygiene.

47. Should any adverse event occur during the proposed clinical trial, the event would be assessed by the Investigator or medical staff at the relevant study site and appropriate medical intervention determined and administered to the participant if necessary. All procedures described in the guidelines for Good Clinical Practice will be followed (Therapeutic Goods Administration 2000).

3.1.8 Record keeping

48. The licence holder will ensure that procedures are in place to account for all GM flu vaccine stocks imported into Australia under the licence. The GM flu vaccines will be accounted for from import to destruction, and records will be made available to the Regulator on request. Records of training of the clinical trial staff and of ongoing monitoring and auditing of trial sites will also be made available to the Regulator on request.

3.2 Limits proposed by the applicant (scope, scale, locations, duration and people)

49. The clinical trials may be conducted at specialised clinical trial facilities and hospitals. The initial trial involving CodaVax and FluMist flu vaccines is proposed to take place in the Q-Pharm clinical trial facility in Brisbane, Queensland, with Q-Pharm Pty Ltd acting as the CRO. Later trials may take place at other sites, with other CROs, possibly including Nucleus Network in Melbourne, Linear Clinical Research Limited in Perth and IDT CMAX in Adelaide.

50. The initial trial of CodaVax will run from the date of issue of the licence until after the required number of trial participants have been enrolled, treated and any follow-up studies undertaken. The applicant intends to enrol up to 100 participants in this initial trial, with $\frac{1}{3}$ receiving the GM CodaVax vaccine, $\frac{1}{3}$ the active comparator (FluMist) and $\frac{1}{3}$ placebo. Later trials, which may include other as yet unspecified SAVE flu vaccines, would include additional participants (approx. 300 to 400), and the SAVE flu vaccines to be trialled may be trivalent or quadrivalent (i.e. containing 3 or 4 GM SAVE flu virus strains). The unspecified SAVE flu vaccine strains will depend on WHO and AIVC advice on the antigen composition of flu vaccines for the current or upcoming flu season for the southern hemisphere. Over the

proposed 5 year timeframe for these trials, up to a total of 500 participants may be enrolled. FluMist would be used as the active comparator in each trial.

3.3 Controls proposed by the applicant to restrict the spread and persistence of the GM flu vaccines and their genetic material in the environment

51. The applicant has proposed a number of controls to limit exposure to the GM flu vaccines, and to restrict their spread and persistence in the environment. These include:

- excluding prospective participants with a known immune deficiency
- all clinical trial staff will have an influenza vaccination one month prior to handling GM flu vaccines
- staff handling the GM flu vaccines will wear and use appropriate protective clothing and equipment
- GM flu vaccines will be administered by appropriately trained medical staff in a clinical setting and in accordance with ICH-GCP and TGA good clinical practice guidelines
- trial participants will be instructed in precautions to minimise interpersonal spread of the GM flu vaccines
- contingency plans will be in place to manage exposure to the GM flu vaccines and treat any flu-related illness that may eventuate
- the GM flu vaccines will be transported and stored in accordance with relevant guidelines and regulations²;
- waste generated at the clinical trial sites will be disposed of in accordance with standard clinical waste disposal practices, as required by the relevant Australian and state legislation
- trial participants will be instructed to place contaminated waste generated at home in a sealed primary container and secondary container before returning it to the clinical site, and
- unused GM flu vaccines will be destroyed on completion of the study.

52. The suitability of these controls and the limits outlined above is assessed in Chapter 3.

Section 4 The parent organism

53. 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 a carrier coughs, sneezes or talks. They are also transmitted when contaminated surfaces, such as hands or tissues, make contact with the mucous membranes.

54. In temperate climates, the annual influenza epidemic peaks during winter while in the tropics, it can occur throughout the 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 2014). Influenza viruses are endemic in Australia, and each year they cause about 13,500

² The Regulator's *Guidelines for the Transport, Storage and Disposal of Genetically Modified Organisms*; IATA Transportation Regulations; National vaccine storage guidelines: Strive for 5, 2nd Edition; and the Standard for the Uniform Scheduling of Medicines and Poisons.

hospitalisations and over 3,000 deaths among Australians aged over 50 years (Department of Health 2015).

55. Detailed information relating to Human influenza A and B viruses can be found in the [Risk Assessment and Risk Management Plan for DIR 137](#), available from the OGTR website.

Section 5 GM flu vaccine viruses – nature and effect of genetic modifications

5.1 Introduction

56. The underlying premise of nasal vaccination with live attenuated flu vaccines is that exposure to influenza viruses through the natural route of infection would induce immunity at the most probable site of infection. The attenuation of the GM flu vaccines means that they are expected to cause less severe disease, and have limited replication in the mucosa of the upper respiratory tract, while still eliciting a strong immune response. The two types of GM flu vaccine, SAVE flu vaccines (including CodaVax) and FluMist, are attenuated in different ways.

5.2 CodaVax and other SAVE flu vaccine viruses

5.2.1 Method of genetic modification

57. In the GM CodaVax and other SAVE flu vaccines, the haemagglutinin and neuraminidase segments of the parent virus will be modified by incorporating a large number of point mutations. The SAVE design strategy involves determining alternative HA and NA gene sequences which encode the same amino acid sequences as the original HA and NA genes of a specific flu strain, by incorporating codons and codon-pairs that are synonymous (i.e. they encode the same amino acid) but are known to be rare in humans. As an example, the CodaVax vaccine strain, based on the pandemic A/California/07/2009 (H1N1) influenza strain, has a total of 639 altered nucleotides in the HA and NA segments (Figure 2).

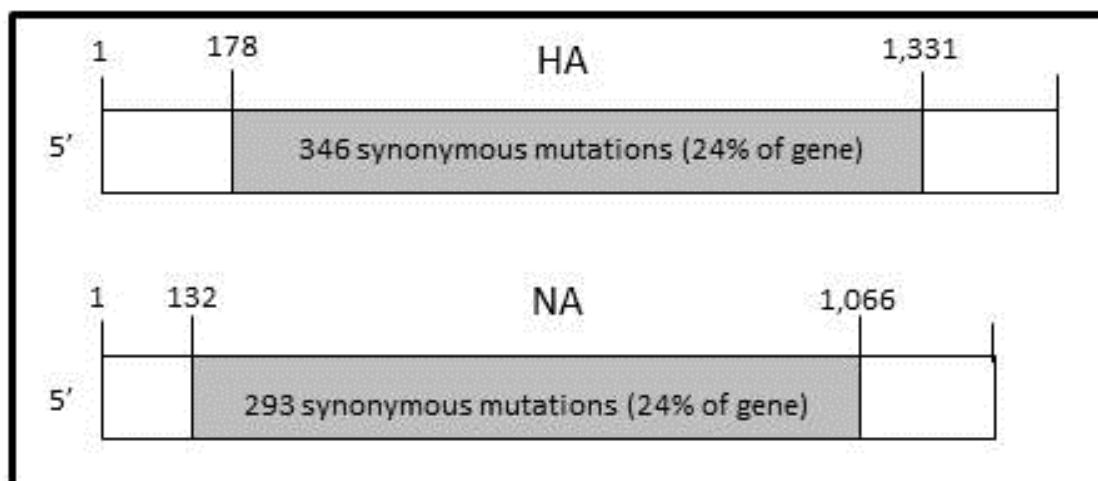


Figure 2. The deoptimised segments of CodaVax, HA and NA gene segments of A/California/07/2009 (H1N1).

58. The genetic modifications in the SAVE flu vaccines are achieved via *de novo* DNA synthesis of a series of oligonucleotides incorporating the desired nucleotide substitutions, and assembly of these into full HA and NA genome segments³.

³ The specific details relating to the genome modifications and vaccine production to produce the CodaVax and other SAVE flu vaccines are under consideration as Confidential Commercial Information (CCI) under section 185 of the Act. Any confidential information will be made available to the prescribed experts and agencies.

59. In addition to the modified HA and NA segments, the entire (unaltered) genome segments for PB1, PB2, PA, M, NP, NS1 of the wild-type target virus are synthesized in the same way. These full complement of eight genome segments are then transfected into Madin-Darby Canine Kidney (MDCK) cells, where they are able to replicate to produce new virions.

5.2.2 Effect of genetic modification

60. Due to its potential effect on gene expression, altering codon pair frequencies towards those that are disfavoured in their hosts has recently been advocated as a novel strategy to reduce RNA virus replication (Coleman et al. 2008; Wimmer et al. 2009; Mueller et al. 2010; Martrus et al. 2013; Yang et al. 2013; Le Nouen C. et al. 2014; Ni et al. 2014).

61. In one of the first examples of codon pair deoptimisation (CPD) to reduce viral replication, Coleman et al. generated synthetic poliovirus capsid gene sequences containing codon pairs that were specifically disfavoured in human coding sequences (Coleman et al. 2008). Virus generated from these mutants showed a remarkably attenuated replication phenotype attributed by the authors to impaired translation efficiency.

62. CPD has since been developed as a strategy for the production of a wide range of other live attenuated virus vaccines including influenza A virus, porcine reproductive and respiratory syndrome virus, human immunodeficiency virus type 1 (HIV-1) and respiratory syncytial virus (Mueller et al. 2010; Martrus et al. 2013; Yang et al. 2013; Le Nouen C. et al. 2014; Ni et al. 2014).

63. A study investigating the codon deoptimisation of the HA and NA segments in the A/Puerto Rico/8/34 (H1N1) flu strain [(PR8-(HA+NA)^{Min.}] based on the SAVE strategy has been recently published (Yang et al. 2013). This study presented data that the PR8-(HA+NA)^{Min.} flu strain produced significantly decreased HA protein levels and only slightly decreased HA and NA mRNA levels in MDCK tissue culture cells (the protein level for NA was not determined) (Yang et al. 2013). This indicates that the most likely mechanism for the attenuation achieved by codon deoptimisation of HA and NA segments is reduced protein translation of the recoded mRNA. It is surmised in a recent review that the attenuation is a consequence of the paucity of flu glycoproteins HA and NA during infection, which results in limited or minimal virion formation and release (Baker et al. 2015).

64. In the Yang et al. (2013) study, the PR8-(HA+NA)^{Min.} flu strain also demonstrated growth attenuation in the A549 human lung adenocarcinoma epithelial cell line, reduced pathogenesis in BALB/c mice and protective immunity against lethal challenge from wild-type or heterologous influenza strains in mice.

65. For CodaVax, the incorporation of substantial silent mutations to the HA and NA segments results in decreased HA and NA protein expression and reduced virulence (e.g. attenuation)⁴. It is envisaged that SAVE flu vaccines based on other flu strains will have a similar phenotype of reduced HA and NA protein expression and attenuation.

66. The pathogenicity of the CodaVax vaccine was tested in DBA-2 mice, which are highly sensitive to wild-type A/California/07/2009 (H1N1) infection (Pica et al. 2011). DBA-2 mice were inoculated with CodaVax or the wild-type virus. The wild-type virus was confirmed to be highly virulent in DBA-2 mice, causing mortality with a LD₅₀ of 3.2 x 10² pfu. In contrast, the CodaVax virus did not cause any mortality in DBA-2 mice at the highest dose tested (10⁶ pfu), indicating over a 10,000-fold reduction in pathogenicity.

67. The ability of CodaVax to induce protective immunity was examined in a mouse challenge study using five- to six-week old BALB/c mice (Figure 3). In this experiment, one

⁴ The specific details relating to reduced protein expression and attenuation of the CodaVax vaccine virus are under consideration as Confidential Commercial Information (CCI) under section 185 of the Act. Any confidential information will be made available to the prescribed experts and agencies.

group of mice was inoculated intranasally with 10 pfu of CodaVax, another with 100 pfu and a third group was not inoculated (mock/control group). Twenty eight days after inoculation, the animals were challenged with 1000 x LD₅₀ of wild-type A/California/07/2009 (H1N1) (3 x 10⁵ pfu). All inoculated mice maintained their weight and survived whereas all mice in the control group suffered rapid weight loss and succumbed to infection by 9 days post challenge.

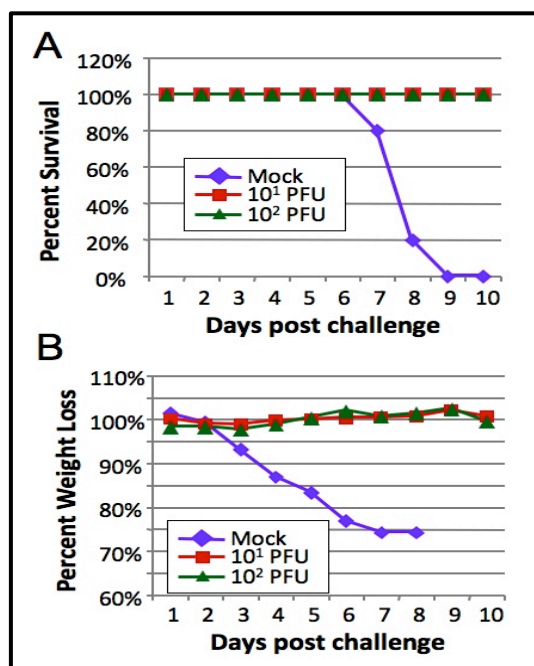


Figure 3. Ultra-low dose protection from lethal flu challenge in mice vaccinated with CodaVax.

BALB/c mice were inoculated with 10 pfu or 100 pfu of CodaVax, or mock inoculated, and challenged 28 days later with 3 x 10⁵ pfu of wild-type A/California/07/2009. Mice were monitored for survival (A) and weight (B).

68. Given that ferrets serve as a model organism for the study of human influenza (see [DIR 137 RARMP](#), paragraph 100), in a study conducted by the IIT Research Institute (Chicago, IL, USA), ferrets were vaccinated with a single intranasal dose of CodaVax at 5 x 10³ pfu or FluMist (5 x 10³ pfu, low dose; or 10⁷ pfu, high dose). No ferrets in any group developed fever, indicating a high degree of safety for each of the GM flu vaccines tested. Similarly, ferrets vaccinated with a single intranasal dose of CodaVax (5 x 10³ pfu) had no statistically significant difference in weight compared to mock vaccinated ferrets, whereas ferrets inoculated with 5 x 10³ pfu of the parent flu strain became ill and lost weight.

5.2.3 Characterisation of the CodaVax and other SAVE flu vaccines

Genotype stability and molecular characterisation

69. The GM CodaVax vaccine virus has over 500 silent mutations and is highly unlikely to revert to the wild-type sequence. Several studies involving codon deoptimisation for the attenuation of poliovirus, arenavirus and porcine reproductive and respiratory syndrome virus have demonstrated that the introduction of the large number of silent mutations does not decrease the genetic stability of the virus (Coleman et al. 2008; Ni et al. 2014; Cheng et al. 2015).

70. The genetic stability of CodaVax was examined in the MDCK cell-line used for the production of SAVE influenza vaccines. No new mutations were found in the HA and NA segments of the CodaVax vaccine stock after 10 passages at low multiplicity of infection.

71. The applicant has reported that CodaVax vaccine that was passaged 50 or 100 times in the production cell line was found to have no increase in virulence (LD₅₀) when tested in BALB/c mice, although the specifics of the experimental testing in mice were not provided.

The applicant reported that there were “unintended” mutations found in the CodaVax vaccine genome after 100 passages in the production cell line. The applicants also reported that passaging the wild-type virus A/California/07/2009 (H1N1) 100 times in the same cell line produced a similar number of mutations. These findings indicate there was no discernible change in the genetic stability of the CodaVax vaccine in comparison to the wild-type virus in the production cell line. The finding of mutations in both the CodaVax vaccine and wild-type A/California/07/2009 (H1N1) genomes after 100 passages in the production cell line is not unexpected for single-stranded RNA viruses, due to their naturally high replication error rate (see [DIR 137 RARMP](#), Chapter 1, Section 4.8).

Shedding

72. No human shedding studies of the CodaVax vaccine virus (or other SAVE flu vaccines) have been performed as this vaccine is yet to be administered to human subjects. As these vaccines are live attenuated influenza viruses, designed to induce immune protection by replication in cells lining the nasopharynx, some shedding of the vaccine virus in nasal secretions is expected to occur for some period following vaccination.

73. In a non-clinical study in ferrets, the applicant has stated that shedding of the CodaVax vaccine virus occurred up to 4 days after administration. There was no evidence of viral shedding after 4 days, with shedding examined for 6 days after administration.

Transmissibility

74. No human or animal transmissibility studies of CodaVax vaccine (or other SAVE flu vaccines) were provided in the application.

5.3 FluMist flu vaccine viruses (the active comparator for the SAVE flu vaccines)

75. The proposed FluMist seasonal GM flu vaccines are tetravalent live attenuated vaccines. They contain four GM attenuated flu vaccine strains to induce immunity against four targeted seasonal strains. Detailed information relating to the genetic modifications and characterisation of FluMist can be found in the [Risk Assessment and Risk Management Plan for DIR 137](#).

Section 6 Receiving environment

76. The receiving environment forms part of the context for assessing risks associated with dealings with GMOs (OGTR 2013). It influences the likelihood of the GMOs dispersing or persisting beyond the confines of the clinical trial.

6.1 Site of release

77. The intended primary receiving environment would be the nose, nasal turbinates and nasopharynx of trial participants, to be delivered either via a nasal sprayer as a high speed aerosol or using a dropper.

78. The secondary receiving environment would be the room where the vaccine is administered.

79. The principal route by which the GM flu vaccine strains may enter the wider environment is release from trial participants following inoculation e.g. the recipient sneezing or shedding.

6.2 Related viral species in the receiving environment

80. The presence of related viral species may offer an opportunity for the horizontal transfer of any introduced genetic material from the GM flu vaccine strains to other organisms in receiving environment.

81. 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.

82. The *Orthomyxoviridae* family 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 cannot undergo homologous recombination. The segmented genome allows horizontal gene transfer through reassortment.

83. Reassortment only occurs with influenza viruses of the same type. Therefore influenza A virus and influenza B virus do not reassort with each other, with influenza C virus or with other *Orthomyxoviridae*.

84. The most closely related species to *Influenzavirus A* and *Influenzavirus B* is *Influenzavirus C*. Other members of the *Orthomyxoviridae* family include *Isavirus* (infects salmon), *Thogotovirus*, *Quarantivirus* and *Lake Chad virus* (arbovirus). The transfer of genetic material between members of the *Orthomyxoviridae* has not been reported.

6.3 Similar genetic material in the environment

85. The balance of a system could be perturbed by the introduction of new genetic material through horizontal gene transfer or through the release of GM flu vaccine strains into the environment. However, the effect of this perturbation would be relatively small if the genetic material was previously present in the system and did not confer any selective advantage to an organism that gained this genetic material.

86. The GM CodaVax and other SAVE flu vaccines will contain codon-deoptimised HA and NA genomic segments of the parental (targeted) flu strains, encoding the same HA and NA proteins as the corresponding genome segments in the parental flu strains. The parental strain for CodaVax is the A/California/07/2009 (H1N1) strain. This influenza strain is widespread in the environment, and has been the target for the H1N1 component of the seasonal influenza vaccine for the past three seasons.

87. Parental flu strains for other SAVE flu vaccines will depend on WHO and AIVC advice on the antigen composition of flu vaccines for the current or upcoming flu season for the southern hemisphere. Whatever strains are recommended, they will be widely circulating in the human population, predicted to be the most common in the upcoming influenza season.

88. The haemagglutinin and neuraminidase segments introduced into the FluMist vaccine strains would likewise be widespread in the environment, as they are also derived from the target strains recommended by the WHO's Global Influenza Surveillance and Response System.

89. All of the genes and genomic segments in the FluMist vaccine strains would be functionally similar to ones present in other influenza viruses.

6.4 Alternate hosts

90. 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.

91. The principal reservoir of human influenza A viruses is humans, but new human subtypes can arise from avian reservoirs. Wild waterfowl are the primary reservoir for most subtypes of influenza A viruses and the most likely progenitor of influenza A viruses that infect all other animals, including swine, horses, dogs and mustelids (eg mink, ferrets).

92. Influenza B viruses have a limited host range with humans and seals being the most common hosts (Osterhaus et al. 2000). There are reports on the seroconversion of dogs

inoculated with influenza B viruses but these are contradictory (Rimmelzwaan et al. 2006; Kawano et al. 1978).

93. Guinea pigs and ferrets are the species most susceptible to wild-type human influenza, but are unlikely to be infected through shedding 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 (see [DIR 137 RARMP](#), Chapter 1, Section 4.9), and therefore are unlikely to be infected through shedding of the GM flu vaccine viruses.

Section 7 Previous Australian and international approvals

7.1 Australian authorisations

7.1.1 Previous approvals by the Gene Technology Regulator

94. The Regulator has not previously approved any DIR or Dealings not involving Intentional Release licences for dealings with the GM CodaVax or other SAVE flu vaccines.

95. The Regulator recently issued a DIR licence (DIR 137) for the commercial supply of FluMist flu vaccines which are proposed to be used as a comparator in this clinical trial.

7.1.2 Approvals by other government agencies

96. At this time, the GM flu vaccines proposed for use in the clinical trials (CodaVax, other SAVE flu vaccines and FluMist) have not been approved for use in Australia by the TGA.

7.2 International authorisations and experience

97. The applicant has indicated that there have not been any overseas authorisations or applications for the evaluation or clinical trial of the GM CodaVax or other SAVE flu vaccines.

98. AstraZeneca's FluMist vaccines are available commercially in several other jurisdictions as shown in Table 1. The trivalent version of the seasonal vaccine was first released in the 2003/2004 northern hemisphere influenza season. The release of the quadrivalent vaccine occurred after the WHO recommended a second influenza B virus strain for targeting by vaccines.

99. As shown in Table 1, in each of the three jurisdictions where they are commercially available, the seasonal GM flu vaccines have been assessed twice, once for the release of the trivalent vaccine and once for the release of the quadrivalent vaccine. There was a 10-year gap between the releases of these two vaccine versions in the USA and shorter intervals in the EU and Canada.

Table 1 Overseas marketing approvals for AstraZeneca's GM flu vaccines

Released in*	Jurisdiction	Vaccine type	Trade Name
2003/2004	USA	trivalent	FluMist
2012/2013	EU	trivalent	Fluenz
2010/2011	Canada	trivalent	FluMist
2013/2014	USA	quadrivalent	FluMist Quadrivalent
2014/2015	Canada	quadrivalent	FluMist Quadrivalent
2014/2015	EU	quadrivalent	Fluenz Tetra

*Northern hemisphere influenza season

Chapter 2 Risk assessment

Section 1 Introduction

100. 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 4). Risks are identified within the context established for the risk assessment (see Chapter 1), taking into account current scientific and technical knowledge. A consideration of uncertainty, in particular knowledge gaps, occurs throughout the risk assessment process.

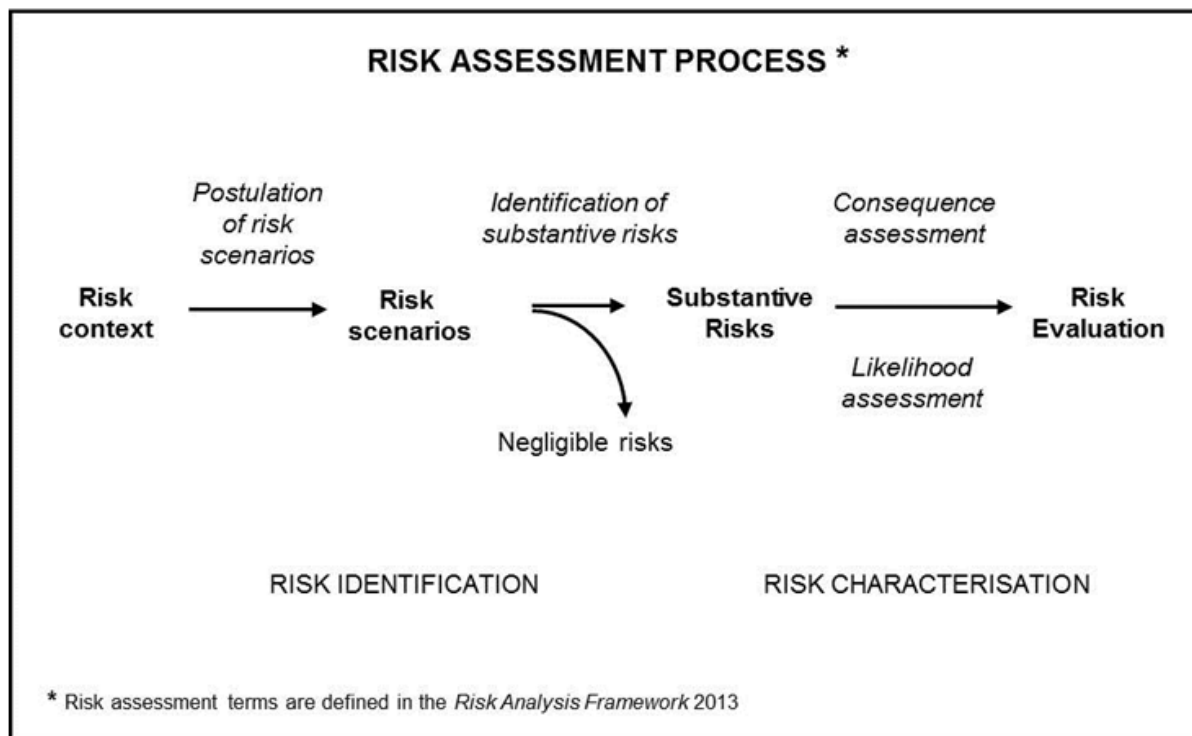


Figure 4. The risk assessment process

101. Initially, risk identification considers a wide range of circumstances whereby the GMO, or the introduced genetic material, could come into contact with people or the environment. Consideration of these circumstances leads to postulating plausible causal or exposure pathways that may give rise to harm for people or the environment from dealings with a GMO (risk scenarios) in the short and long term.

102. Postulated risk scenarios are screened to identify substantive risks that warrant detailed characterisation. A substantive risk is only identified for further assessment when a risk scenario is considered to have some reasonable chance of causing harm. Pathways that do not lead to harm, or could not plausibly occur, do not advance in the risk assessment process.

103. A number of risk identification techniques are used by the Regulator and staff of the OGTR, including checklists, brainstorming, reported international experience and consultation (OGTR 2013). In conjunction with these techniques, risk scenarios postulated in previous RARMPs prepared for licence applications of the same and similar GMOs are also considered.

104. Substantive risks (i.e. those identified for further assessment) are characterised in terms of the potential seriousness of harm (Consequence assessment) and the likelihood of harm (Likelihood assessment). The level of risk is then estimated from a combination of the Consequence and Likelihood assessments. Risk evaluation then combines the Consequence

and Likelihood assessments to determine level of risk and whether risk treatment measures are required. The potential for interactions between risks is also considered.

Section 2 Risk Identification

105. Postulated risk scenarios incorporate three components (Figure 5):

- i. The source of potential harm (risk source)
- ii. A plausible causal linkage to potential harm (causal pathway); and
- iii. Potential harm to an object of value, people or the environment.

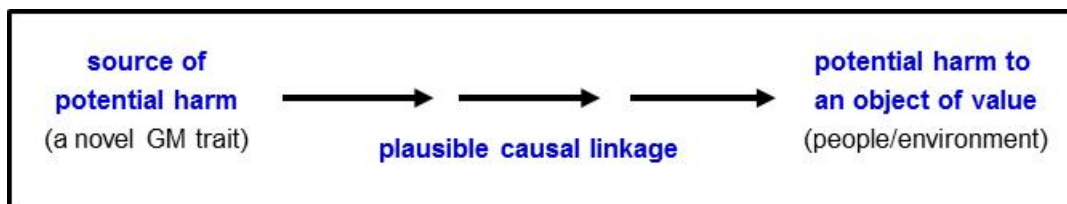


Figure 5. Risk scenario

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

- the dealings proposed by the applicant, which are import, conduct experiments with, transport or dispose of the GMOs and the possession (including storage), supply and use of the GMOs in the course of any of these dealings;
- the proposed limits, including the extent and scale of the proposed dealings;
- the proposed controls to restrict the spread and persistence of the GMO;
- characteristics of the parent organism;
- routes of exposure to the GMOs, the introduced genes and gene products;
- potential effects of the introduced genes and gene products expressed in the GMOs;
- potential exposure to the introduced genes and gene products from other sources in the environment; and
- the environment at the site(s) of release.

107. As discussed in Chapter 1, Section 2, the TGA, the trial sponsor, the investigators and HREC all have roles in ensuring the safety of participants under the *Therapeutic Goods Act 1989*, and the use of a therapeutic good in a clinical trial must be in accordance with the *National Statement on the Ethical Conduct in Research Involving Humans* (National Health and Medical Research Council 2013). Therefore, risk scenarios in the current assessment focus primarily on risks posed to people other than those participating in the clinical trial, and to the environment.

108. Based on the dealings, limits and controls proposed by the applicant, ten risk scenarios were postulated and screened to identify substantive risks. They are summarised in Table 2, where circumstances that share a number of common features are grouped together in broader risk categories. Two of these risk scenarios were identified as posing substantive risks which warranted further assessment. More detail on the scenarios not identified as substantive risks is provided later in this Section, while the substantive risks are characterised in Section 3 of this chapter.

Table 2 Summary of risk scenarios from dealings with the GMO

Risk Scenario				Substantive risk?	Reasons
#	Risk source	Causal pathway	Potential harm		
Ill health following direct exposure to the GM CodaVax or FluMist flu vaccine preparations					
1	GM CodaVax and FluMist vaccines	i. Exposure of persons dispensing or administering the GMO at a clinical site or laboratory via contact with abraded skin or mucous membranes (esp. eyes) ↓ ii. Establishment of viral infection.	Ill health	No	<ul style="list-style-type: none"> The GM viruses would be dispensed in a BSC by staff wearing appropriate PPE and in accordance with approved clinical site procedures. The GMOs would be administered by trained medical staff wearing appropriate PPE and in accordance with Standard Universal Precautions and national guidelines. All clinical trial staff will have an influenza vaccination one month prior to handling the vaccines. The dose received through accidental exposure would be substantially less than that administered to trial participants. Influenza viruses desiccate rapidly under ambient conditions. The GM flu vaccines have been shown to be attenuated with respect to their ability to replicate.
2	GM CodaVax and FluMist vaccines	i. Unused GMO or waste containing the GMO disposed of from clinical site or laboratory ↓ ii. Exposure of persons handling waste containing the GMO ↓ iii. Establishment of viral infection.	Ill health	No	<ul style="list-style-type: none"> Unused GMOs and contaminated waste will be placed in appropriately labelled clinical waste containers and disposed of as infectious clinical waste. As noted in Scenario 1, inadvertent exposure to the GMOs is likely to involve a low dose; the GM flu vaccines are attenuated; and Influenza viruses desiccate rapidly under ambient conditions.

Risk Scenario				Substantive risk?	Reasons
#	Risk source	Causal pathway	Potential harm		
3	GM CodaVax and FluMist vaccines	i. Exposure of people or animals to the GM virus due to unintentional release during transport or storage ↓ ii. Establishment of viral infection.	Ill health	No	<ul style="list-style-type: none"> • Transport to clinical sites will follow appropriate standards for medical products. • Storage will be at secure clinical facilities. • The GMOs will be double-contained for internal transport within clinical sites and a spills procedure will be in place. • All stocks of the GMOs will be accounted for and all unused GMOs will be destroyed when the study is complete. • As noted in Scenario 1, inadvertent exposure to the GMOs is likely to involve a low dose; the GM flu vaccines are attenuated; and Influenza viruses desiccate rapidly under ambient conditions.
Ill health following indirect exposure to the GM CodaVax or FluMist flu vaccines					
4	GM CodaVax and FluMist vaccines	i. Treatment of trial participant with the GMO ↓ ii. Samples containing GMO collected from trial participant ↓ iii. Laboratory staff exposed to GMO during analysis ↓ iv. Establishment of viral infection.	Ill health	No	<ul style="list-style-type: none"> • Sample testing would be conducted by qualified personnel in pathology or other testing laboratories, which are required to adhere to national standards for handling of infectious substances. • As noted in Scenario 1, inadvertent exposure to the GMOs is likely to involve a low dose; the GM flu vaccines are attenuated; Influenza viruses desiccate rapidly under ambient conditions.

Risk Scenario				Substantive risk?	Reasons
#	Risk source	Causal pathway	Potential harm		
5	GM CodaVax and FluMist vaccines	i. Treatment of trial participant with the GMO ↓ ii. Trial participant sheds the GMO ↓ iii. Exposure of clinical/hospital staff and other people (e.g. carers or household contacts), other than at-risk people, through contact with trial participant or contaminated items (e.g. contaminated tissues/waste) ↓ iv. Establishment of viral infection.	Ill health	No	<ul style="list-style-type: none"> • Patient management would be by trained medical staff in clinical facilities in accordance with Standard Universal Precautions and national guidelines. • Trial participants will be instructed in well-established hygiene practices known to minimise inadvertent transmission of flu viruses. • Patients will be instructed to use tissues to collect any respiratory secretions as a result of sneezing, coughing or eye secretions, and to seal contaminated waste in a primary container (e.g. sealable plastic bag) and place this within a biohazard container, to be returned to the clinical site. • As noted in Scenario 1, inadvertent exposure to the GMOs is likely to involve a low dose; the GM flu vaccines are attenuated; and Influenza viruses desiccate rapidly under ambient conditions.
6	GM CodaVax and FluMist vaccines	i. Treatment of trial participant with the GMO ↓ ii. Trial participant sheds the GMO ↓ iii. Exposure of at-risk people (such as immunocompromised persons; e.g. carers, household contacts, clinical patients) through contact with trial participant or contaminated items (e.g. contaminated tissues/waste) ↓ iv. Establishment of viral infection.	Ill health	Yes	<ul style="list-style-type: none"> • Trial participants may shed GM virus after vaccine administration. • At-risk individuals are not proposed to be excluded from caring for patients. • Trial participants are not proposed to be advised to avoid contact with at-risk people following inoculation with the GMOs. • There is uncertainty about the consequences for at-risk people exposed to the GM virus. See Section 3.1 for risk characterisation.

Risk Scenario				Substantive risk?	Reasons
#	Risk source	Causal pathway	Potential harm		
7	GM CodaVax and FluMist vaccines	i. Treatment of trial participant with the GMO ↓ ii. Trial participant sheds the GMO ↓ iii. Exposure of animals (e.g. domestic pets and wild animals) through contact with trial participant or contaminated items (e.g. contaminated tissues/waste) due to trial participant shedding the GMO ↓ iv. Establishment of viral infection.	Ill health	No	<ul style="list-style-type: none"> • Trial participants will be instructed in well-established hygiene practices known to minimise inadvertent transmission of flu viruses. • Patients will be instructed to use tissues to collect any respiratory secretions as a result of sneezing, coughing or eye secretions to seal contaminated waste in a primary container (e.g. sealable plastic bag) and placed within a biohazard container, to be returned to the clinical site. • Influenza viruses are generally host specific (see DIR 137 RARMP, Chapter 1, Section 4.9). • As noted in Scenario 1, inadvertent exposure to the GMOs is likely to involve a low dose; the GM flu vaccines are attenuated; and Influenza viruses desiccate rapidly under ambient conditions.
Ill health following direct or indirect exposure to other GM SAVE flu vaccines					
8	Unspecified GM SAVE flu vaccines	i. Exposure, leading to infection Risk scenarios 1-7 as described above.	Ill health	Yes	<ul style="list-style-type: none"> • As the attenuation of these SAVE flu vaccine strains has not been confirmed, there is uncertainty about the consequences for people and animals exposed to them. See Section 3.1 for risk characterisation.

Risk Scenario				Substantive risk?	Reasons
#	Risk source	Causal pathway	Potential harm		
Horizontal transfer of genes or genetic elements					
9	GM CodaVax, unspecified SAVE flu vaccines or FluMist vaccines	i. Exposure of people or animals to the GM virus leading to infection (see risk Scenarios 1-8) ↓ ii. Person or animal also infected with contemporary influenza virus carrying a different haemagglutinin and/or neuraminidase from the vaccine strains ↓ iii. Both viruses infect and replicate in the same host cell ↓ iv. Reassortment between viral genomes takes place and recombinant virus propagates ↓ v. Establishment of viral infection.	Ill health	No	<ul style="list-style-type: none"> Co-infection of a host cell by the GMOs and another strain would be uncommon. For CodaVax and other SAVE flu vaccines Any possible reassortment involving the HA and NA genomic segments of the CodaVax or SAVE flu vaccines would not result in a virus that is more virulent than circulating <i>wild-type</i> virus. For FluMist <ul style="list-style-type: none"> The FluMist vaccines strains would not contain any novel genetic material. The introduced haemagglutinin and neuraminidase genome segments are derived from strains predicted to be the most common circulating strains for the season, so do not add any antigenic novelty. Reassortants containing other genome segments from the GMOs are expected to be less virulent than circulating strains.
10	GM CodaVax, unspecified SAVE flu vaccines or FluMist vaccines	i. Trial participant or another person infected with the GMO is infected with an influenza virus of swine or avian origin ↓ ii. Both viruses co-infect the same host cell ↓ iii. GMO and swine/avian influenza virus reassort ↓ iv. Haemagglutinin and/or neuraminidase segment in GMO is replaced with equivalent segment from swine or avian influenza strain ↓ v. Reassortant infects host and recombinant virus propagates ↓ vi. Establishment of viral infection	Ill health	No	<ul style="list-style-type: none"> Co-infection of a host cell by the GMOs and another flu strain would be uncommon. Reassortment involving the HA and NA genomic segments of the CodaVax or SAVE flu vaccines would not result in a virus that is more virulent than reassortants between an avian or pig strain and a circulating flu strain. Reassortants containing other genome segments from the GMOs are expected to be less virulent (FluMist) or no more virulent (CodaVax and SAVE flu vaccines) than reassortments between an avian or pig strain and a circulating flu strain. The FluMist vaccine strains would not contain any novel genetic material, with the introduced haemagglutinin and neuraminidase genome segments derived from strains predicted to be the most common circulating strains for the season. Reassortants containing other genome segments from the GMOs are expected to be less virulent (FluMist) or the same as (CodaVax and SAVE flu vaccines) circulating strains.

2.1 Ill health from exposure to the GM flu vaccines

109. The parent organisms of the GM flu vaccine strains, human influenza A virus and human influenza B virus, are respiratory pathogens. Details on their transmissibility and pathogenicity are given in Chapter 1.

110. Infection is generally the result of inhalation of aerosol droplets containing the virus or of mucosal exposure to contaminated surfaces. The replication of the influenza virus in respiratory epithelial cells results in their apoptosis, as manifested in disease symptoms such as a runny nose, cough and sore throat.

111. Infection with influenza viruses does not result in latent infection or integration into the host genome.

112. CodaVax and SAVE flu vaccines contain a large number of point mutations in the HA and NA genomic segments. These mutations will not alter the HA and NA amino acid (protein) sequences compared to the parental flu strains. Therefore, the toxicity and allergenicity of the modified genes in CodaVax or SAVE flu vaccines and their products were not directly considered but are taken into account in the context of their contribution to ill health.

113. The FluMist vaccine strains are live attenuated influenza viruses with the restricted replicative traits of a cold-adapted parent and the antigenic determinants of a contemporary circulating strain. In the FluMist vaccine strains, the haemagglutinin and neuraminidase segments in a cold-adapted parent virus are replaced by the equivalent segments from a flu strain to be targeted by the vaccine. FluMist vaccine strains have been constructed by reverse genetics (see [DIR 137 RARMP](#), Chapter 1, Section 5.3), but could arise from natural reassortment of the parent strains. The toxicity and allergenicity of the introduced genes in FluMist and their products were not directly considered but are taken into account in the context of their contribution to ill health.

114. Trial participants will be intentionally exposed to the GM flu vaccines. However, a range of other people and animals may be inadvertently exposed – either directly to purified GMO's supplied for use in the study, or to GM virus shed by trial participants.

115. Pathways that could lead to ill health from the GM flu vaccine include:

- exposure of clinical staff administering the GM flu vaccines, other staff or contractors handling the vaccine stock during preparation, administration, transport, storage or disposal;
- exposure of people to GM virus shed from trial participants, including clinical staff caring for participants on return visits to the hospital, other patients, home carers, other household contacts, and other contacts;
- exposure of animals such as domestic pets to GM virus shed from trial participants; and
- exposure of people or animals in the environment to GM virus during disposal.

116. These scenarios that could lead to the development of influenza, resulting in ill health, are discussed below.

2.1.1 Risk scenario 1 – Exposure of persons dispensing or administering the GMO

Risk source	Causal pathway	Potential harm
GM CodaVax and FluMist vaccines	i. Exposure of persons dispensing or administering the GMO at a clinical site or laboratory via contact with abraded skin or mucous membranes (esp. eyes) ↓ ii. Establishment of viral infection.	Ill health

Causal pathway

117. Pharmacy or laboratory staff diluting or dispensing the GMO and clinical staff administering it to trial participants could be exposed via a splash to the eyes or mouth, exposure of abraded skin or mucus membranes to aerosolised vaccine or through contact with contaminated items.

118. The clinical trial will be conducted by appropriately qualified pharmacy and clinical staff who have been specifically trained in the requirements of the study and appropriate precautions (discussed in Chapter 1, Section 3.1). The administration of the GM flu vaccines is under the responsibility of the principal investigator, according to the clinical protocol and in accordance with ICH-GCP (ICH 1996) and TGA Good Clinical Practice guidelines (Therapeutic Goods Administration 2000).

119. Pharmacy or laboratory staff diluting and dispensing CodaVax and FluMist vaccines would be handling the GMO in its most concentrated form. Clinical staff will work in a biological safety cabinet (BSC), wear gloves and use PPE as appropriate based on risk assessment according to relevant institutional policies and procedures, to minimise the potential for inadvertent exposure to the concentrated GM flu vaccines. FluMist is pre-packaged, ready for administration and will not need to be diluted prior to administration.

120. Clinical staff inoculating patients with the GMO will also wear PPE as appropriate based on risk assessment according to relevant institutional policies and procedures, which would provide protection from exposure to the diluted virus solution. Administration of the GMO and subsequent care of inoculated patients will be, at a minimum, in accordance with the Australian Guidelines for the Prevention and Control of Infection in Healthcare (National Health and Medical Research Council 2010). These guidelines aim to reduce transmission of infectious organisms from both recognized and unrecognized sources in the clinical setting. Appropriate practices include hand hygiene, use of PPE as appropriate and based on risk assessment, disposal practices, safe handling of potentially contaminated equipment or surfaces in the patient environment, respiratory hygiene/cough etiquette and correct cleaning and waste management.

121. Influenza viruses are highly susceptible to desiccation due to their lipid envelope. The GM flu viruses would not remain viable for extended periods on open surfaces.

Potential harm

122. Any dose received by accidental exposure to purified virus while diluting, dispensing or administering the GM flu vaccines is likely to be far lower than the dose intentionally administered to trial participants (5×10^3 pfu per 100 μ L).

123. Even if exposure occurred, CodaVax and FluMist vaccines are attenuated and viral replication would be limited in immune-competent people. Additionally, all clinical trial staff will have an influenza vaccination one month prior to handling the vaccines. Since the GMOs will be made to target the same strains as other current flu vaccines, vaccination should be highly effective.

Conclusion

124. Risk scenario 1 is not identified as a substantive risk because the potential for exposure would be minimised by standard handling procedures and specific precautions proposed by the applicant, including use of appropriate PPE in a situation of increased likelihood of exposure. The GM flu vaccines are attenuated and all clinical trial staff will have an influenza vaccination one month prior to handling the vaccines. Therefore, this risk could not be greater than negligible and does not warrant further detailed assessment.

2.1.2 Risk scenario 2 – Exposure of persons to unused GMO or waste containing the GMO

Risk source	Causal pathway	Potential harm
GM CodaVax and FluMist vaccines	i. Unused GMO or waste containing the GMO disposed of from clinical site or laboratory	Ill health
	↓	
	ii. Exposure of persons handling waste containing the GMO	
	↓	
	iii. Establishment of viral infection.	

Causal pathway

125. Clinical and laboratory staff may come into contact with unused GMO or waste contaminated with the GM virus.

126. Individuals who handle vaccines may be inadvertently exposed to the GM flu vaccine strains while disposing of the primary GM flu vaccine container, or used or unused sprayers or droppers containing GM flu vaccine. The locations where these are most likely to occur are:

- Clinical facility/pharmacy where stocks of GM flu vaccines are held
- the room where GM flu vaccines would be prepared
- the room where GM flu vaccines would be administered
- facilities for the disposal of GM flu vaccines and associated clinical waste.

127. Healthcare staff dispose of medical waste routinely and would have standardised procedures for the safe disposal of both used nasal applicators (droppers or sprayers) with residual GM flu vaccine and unused/expired sprayers of GM flu vaccine in accordance with the Australian Guidelines for the Prevention and Control of Infection in Healthcare (National Health and Medical Research Council 2010), ICH-GCP (ICH 1996) and TGA Good Clinical Practice guidelines (Therapeutic Goods Administration 2000).

128. The applicant has indicated that GM flu vaccines stored at the pharmacy may need to be destroyed if its expiry date has passed or when it is superseded by a new seasonal vaccine. The GM flu vaccine would be placed in containers which are security sealed, tagged and loaded into secure destruction bins. The waste contractor would incinerate the waste. Given the GMO stocks are triple contained during waste disposal, they are highly unlikely to leak in a manner that would lead to exposure of waste handlers to an infective dose the GM flu vaccine.

129. The applicant has indicated that all contaminated waste (e.g. gloves, swabs etc.) will be discarded into appropriately-labelled biological waste containers, which would minimise exposure to material contaminated with the GM flu vaccine once it has been discarded.

130. Contaminated waste will be disposed of by each clinical site following standard clinical waste disposal methods (Queensland 2000; EPA Victoria 2009; Victoria 2000; South Australia 2009; West Australia 2004). The Industry Code of Practice for the Management of Clinical and Related Wastes details requirements for clinical waste including waste segregation, packaging, labelling, storage, transport and accountability (Biohazard Waste Industry Australia and New Zealand (BWI) 2010). The clinical waste stream typically involves destruction of infectious waste by incineration, autoclaving or chemical decontamination, which is considered appropriate for disposal of the GMO.

Potential harm

131. As discussed in Risk Scenario 1, for productive infection, individuals must be exposed to an infectious dose. Since each filled sprayer or dropper would contain the infectious dose of

each GM flu vaccine strain, the residual liquid in used flu applicators would not contain a sufficient titre to cause productive infection. The same would apply to secondary waste such as gloves that may be contaminated with the vaccine. Influenza viruses cannot replicate outside a host cell and the residual viruses in the used sprayers or other surfaces could not multiply to reach an infective dose.

132. The GM flu vaccines must be stored frozen or between 2-8°C and requires a well-controlled and uninterrupted sequence of transport and storage to maintain the vaccine. GM flu vaccines slated for destruction would be held at ambient temperature and this would increase their rate of deterioration.

133. Even if an individual was exposed to the GM flu vaccines, they would be attenuated and therefore, less pathogenic than circulating flu strains.

Conclusion

134. Risk scenario 2 is not identified as a substantive risk because the potential for exposure would be minimised by standard practices for handling of clinical waste. The GM flu vaccines are attenuated and inadvertent exposure would involve small quantities only. Therefore, this risk could not be greater than negligible and does not warrant further detailed assessment.

2.1.3 Risk scenario 3 –Exposure of people or animals to the GM virus due to unintentional release during transport or storage

Risk source	Causal pathway	Potential harm
GM CodaVax and FluMist vaccines	i. Exposure of people or animals to the GM virus due to unintentional release during transport or storage	Ill health
	↓	
	ii. Establishment of viral infection	

Causal pathway

135. Staff at clinical sites (who may or may not be involved in the dealings), and people or animals outside of these sites, may come into contact with the GMO due to a spill during transport or storage.

136. Influenza viruses are generally host specific. Anthroponotic transmission of influenza from humans to domestic pets or primates has been known to occur but it is an atypical event (see [DIR 137 RARMP](#), Chapter 1, Section 4.9). The amino acid sequences of the GM viral proteins of the CodaVax vaccine will remain unchanged and will therefore have the same tropism as wild-type influenza virus. For FluMist, the introduced haemagglutinin and neuraminidase genome segments are derived from flu strains predicted to be the most common circulating strains for the season, and therefore do not add any genetic novelty or tropism compared to circulating wild-type influenza virus.

137. As described in Chapter 13.1.4, the SAVE flu vaccines will be supplied in small volumes in sealed vials, and FluMist will be imported in pre-packaged nasal sprayers, labelled to indicate the contents, quantity and clinical trial details according to TGA requirements for human therapeutics. During transport, primary containers will be shipped in sealed plastic bags. Secondary boxes/cartons will be labelled to indicate that they contain GMOs.

138. Transport for the purpose of import and distribution within Australia will be by commercial courier companies experienced in the transport of pharmaceutical products. Commercial courier companies will be responsible for transporting the GM flu vaccines from the point of import directly to the CRO (study site). For transport during import and

distribution to the clinical facilities within Australia, the GM flu vaccines will be packaged to meet the requirements of IATA shipping classification Biological Substance UN 3373, Category B.

139. Once at the pharmacy or final destination, the GM flu vaccines will be stored in a secure location with access limited to the site pharmacist and medical staff according to the *National vaccine storage guidelines: Strive for 5, 2nd Edition* (Department of Health and Ageing 2013) and the *Standard for the Uniform Scheduling of Medicines and Poisons* (Therapeutic Goods Administration 2016).

140. For transport within clinical sites, the GMO will be double-contained in accordance with the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*.

141. The GM flu vaccines must be stored frozen or between 2-8°C and require a well-controlled and uninterrupted sequence of transport and storage to maintain the viability of the vaccine. In the event of a spill, GM flu vaccines exposed to normal environmental conditions, which would increase their rate of deterioration.

142. Any spills occurring in a clinical setting would be disinfected and cleaned in accordance with the Australian Guidelines for the Prevention and Control of Infection in Healthcare (National Health and Medical Research Council 2010).

143. All stocks of the GMOs will be accounted for and all unused GMO will be destroyed when the study is complete.

Potential harm

144. As discussed in Risk Scenario 1, for productive infection, individuals must be exposed to an infectious dose. Even if an individual was exposed to an infectious dose of the GM flu vaccines, the vaccine strains are attenuated, and symptoms of any resulting infection would therefore be less severe than that caused by circulating flu strains.

145. The GM flu vaccines are attenuated compared to the parent viruses (which are widespread in the Australian environment), and therefore would not be expected to replicate to high titres in humans, minimising the likelihood of transmission to animals.

146. Codon and codon pair preferences are highly conserved across related species (e.g. mammals) (Moura et al. 2007; Mueller et al. 2010; Shen et al. 2015) and CodaVax vaccine has been shown to be attenuated in mammals (mice and ferrets). Given this and the large number of codons that have been deoptimised, it is expected that the GM virus will remain attenuated for any other animal species susceptible to human influenza. The GM FluMist vaccine has been shown to be attenuated in a range of animal species and has been in use since 2003 in the USA and 2012 in the EU (see DIR 137 RARMP, Chapter 1, Section 5.5.3).

Conclusion

147. Risk scenario 3 is not identified as a substantive risk because the potential for exposure would be minimised by standard procedures for transport of infectious biological products. The GM flu vaccines are attenuated and would cause less-severe symptoms than circulating flu strains. Therefore, this risk could not be greater than negligible and does not warrant further detailed assessment.

2.1.4 Risk scenario 4 – Exposure of laboratory staff to GMO during analysis

Risk source	Causal pathway	Potential harm
GM CodaVax and FluMist vaccines	i. Treatment of trial participant with the GMO ↓	Ill health
	ii. Samples containing GMO collected from trial participant ↓	
	iii. Laboratory staff exposed to GMO during analysis ↓	
	iv. Establishment of viral infection.	

Causal Pathway

148. Blood and tissue specimens collected from patients will routinely be exported for analysis overseas, but may be analysed in Australia. Influenza virus is primarily a respiratory pathogen and clinical manifestations in severe infections are not necessarily restricted to the respiratory tract. Studies of influenza A experimental infection and naturally infected persons suggest that viremia can occur before symptom onset (Likos et al. 2007).

149. Laboratory staff in Australian facilities could be exposed through trial participant samples by contact with abraded skin or mucous membranes. The applicant has advised that analytical laboratory staff would follow institutional Standard Operating Procedures in place for the safe handling and disposal of clinical and diagnostic specimens.

150. The National Pathology Accreditation Advisory Council plays a key role in ensuring the quality of Australian pathology services and is responsible for the development and maintenance of standards and guidelines for pathology practices. The standards include safety precautions to protect the safety of workers from exposure to infectious microorganisms in pathology laboratories. Australian pathology laboratories conform to AS/NZS 2243.3:2010 Safety in Laboratories Part 3: Microbiological Safety and Containment, which stipulates that human clinical and diagnostic specimens be handled in PC2 containment as a minimum standard. As unmodified influenza is classified as a Risk Group 2 organism in Australia, this would provide sufficient protection from exposure to the GM virus.

Potential harm

151. As discussed in Risk Scenarios 1 and 2, for productive infection, individuals must be exposed to an infectious dose. Clinical samples would not be expected to contain a sufficient titre to cause productive infection. Influenza viruses cannot replicate outside a host cell and the residual viruses in the clinical samples could not multiply to reach an infective dose.

152. Even if an individual was exposed to the GM flu vaccines, they would be attenuated and therefore, less pathogenic than circulating flu strains.

Conclusion

153. Risk scenario 4 is not identified as a substantive risk because the potential for exposure would be minimised by handling the GMO according to national standards that require PC2 containment and PC2 work practices. In addition, the GMO is likely to be attenuated and inadvertent exposure would involve small quantities of GM virus. Therefore, this risk could not be greater than negligible and does not warrant further detailed assessment.

2.1.5 Risk scenario 5 – Exposure of clinical staff and other than at-risk people to GM virus due to shedding of the GMO

Risk source	Causal pathway	Potential harm
GM CodaVax and FluMist vaccines	i. Treatment of trial participant with the GMO ↓	Ill health
	ii. Trial participant sheds the GMO ↓	
	iii. Exposure of clinical/hospital staff and other people (e.g. carers or household contacts), other than at-risk people, through contact with trial participant or contaminated items (e.g. contaminated tissues/waste) ↓	
	iv. Establishment of viral infection.	

Causal pathway

154. Trial participants inoculated with the GM flu vaccines will be required to return to the hospital for assessment and follow-up testing. The GM flu vaccines contain live, attenuated influenza virus intended to induce immune protection by viral replication in cells lining the nasopharynx. The presence of influenza vaccine virus in nasal secretions is expected to occur for some period, possibly up to one week, following administration. Clinical staff interacting with trial participants or collecting samples, other hospital patients and other people could be exposed to GM virus shed by trial participants.

155. Trial participants will be required to follow well-established hygiene practices known to minimise transmission of flu virus. These practices will be explained to prospective participants during initial screening and anyone unwilling or unable to comply will not be enrolled.

156. Patients will be instructed to use tissues to collect any respiratory secretions as a result of sneezing, coughing or eye secretions, to seal contaminated waste in a primary container (e.g. sealable plastic bag) and place these within a biohazard container provided by the applicant. The biohazard containers are to be returned by the trial participant to the clinical site for disposal as clinical waste.

157. Care of and sample collection from trial participants in the clinical setting will be in accordance with Universal Standard Precautions at a minimum (see paragraph 42).

Potential harm

158. As discussed in Risk scenarios 1 and 2, the GM virus is attenuated and is less pathogenic than circulating flu strains. It is expected that any GM viral replication would be limited in immune-competent people.

159. Any accidental exposure to the GM virus from trial participants shedding the GM flu vaccines is likely to be far lower than the dose intentionally administered to trial participants.

Conclusion

160. Risk scenario 5 is not identified as a substantive risk because the potential for exposure would be minimised as trial participants will be required to follow well-established hygiene practices known to minimise inadvertent transmission. Inadvertent exposure to the GMO virus is likely to be minimal as the GM virus is attenuated and unable to replicate efficiently. Therefore, this risk could not be greater than negligible and does not warrant further detailed assessment.

2.1.6 Risk scenario 6 – Exposure of at-risk people to GM virus due to shedding by trial participants

Risk source	Causal pathway	Potential harm
GM CodaVax and FluMist vaccines	i. Treatment of trial participant with the GMO ↓	Ill health
	ii. Trial participant sheds the GMO ↓	
	iii. Exposure of at-risk people (such as immunocompromised persons; e.g. carers or household contacts, clinical patients) through contact with trial participant or contaminated items (e.g. contaminated tissues/waste) ↓	
	iv. Establishment of viral infection	

161. Risk scenario 6 was identified as posing a substantive risk which warranted further assessment. Detailed characterisation of this risk scenario is provided in Section 3 of this chapter.

2.1.7 Risk scenario 7 – Exposure of animals to GM virus due to shedding of the GMO

Risk source	Causal pathway	Potential harm
GM CodaVax and FluMist vaccines	i. Treatment of trial participant with the GMO ↓	Ill health
	ii. Trial participant sheds the GMO ↓	
	iii. Exposure of animals (e.g. domestic pets and wild animals) through contact with trial participant or contaminated items (e.g. contaminated tissues/waste) ↓	
	iv. Establishment of viral infection.	

Causal pathway

162. The presence of influenza vaccine virus in nasal secretions is expected to occur for some period, possibly up to one week following vaccination. Animals could be exposed to GM virus shed by the trial participant.

163. Influenza viruses are generally host specific. Anthroponotic transmission of influenza from humans to domestic pets or primates has been known to occur but it is an atypical event (see [DIR 137 RARMP](#), Chapter 1, Section 4.9).

164. The amino acid sequences of the GM viral proteins of the CodaVax vaccine will remain unchanged and will therefore have the same tropism as wild-type influenza virus.

165. As discussed in Risk scenario 5, trial participants will be required to follow well-established hygiene practices known to minimise transmission of the virus. Patients will also be instructed in practices for disposal of respiratory secretion to minimise potential exposure.

Potential harm

166. As discussed in Risk scenarios 1, 2 and 3, the GM viruses are attenuated and are less pathogenic than circulating flu strains.

167. Any accidental exposure of animals to the GM virus from trial participants shedding the GM flu vaccines is likely to be far lower than the infective dose.

Conclusion

168. Risk scenario 7 is not identified as a substantive risk because influenza viruses are generally host specific and the potential for exposure would be minimised by the use of established hygiene practices. Trial participants will be instructed to follow clearly-defined hygiene practices to minimise inadvertent transmission. Inadvertent exposure to the GMO virus is likely to involve a low dose and the GM virus is attenuated and unable to replicate efficiently. Therefore, this risk could not be greater than negligible and does not warrant further detailed assessment.

2.1.8 Risk scenario 8 – Direct or indirect exposure to unspecified GM SAVE flu vaccines.

Risk source	Causal pathway	Potential harm
Unspecified GM Save flu vaccines	i. Risk scenarios 1-7 as described above	Ill health

169. Risk scenario 8 was identified as posing a substantive risk which warranted further assessment. Detail characterisation of this risk scenario is provided in Section 3 of this chapter.

2.2 Unintended changes in viral characteristics

170. Horizontal gene transfer (HGT) is the stable transfer of genetic material from one organism to another without reproduction (Keese 2008). All genes within an organism, including those introduced by gene technology, can be transferred to another organism by HGT. HGT itself is not considered an adverse effect, but an event that may or may not lead to harm. A gene transferred through HGT could confer a novel trait to the recipient organism, through expression of the gene itself or through changes to expression of endogenous genes. The novel trait may result in negative, neutral or positive effects.

171. Influenza A viruses can undergo reassortment with other influenza A viruses, and influenza B viruses can undergo reassortment with other influenza B viruses. In contrast, reassortment between influenza A viruses and influenza B viruses does not occur and will not be considered further. Influenza viruses do not undergo homologous recombination as they have single-stranded genomes, and this will not be considered further.

172. All the genes and genomic segments in the FluMist vaccines would be derived from existing non-GM flu strains (either the parent attenuated vaccine strains or circulating strains) and therefore the GM flu vaccine strains do not introduce any novel genetic material for HGT.

173. The HA and NA genomic segments in the CodaVax and other SAVE flu vaccines would be derived from existing non-GM flu strains (circulating strains). The HA and NA genomic segments will be modified by directed mutagenesis and therefore the CodaVax and SAVE flu vaccine strains will introduce novel genetic material for HGT.

174. Reassortment, which may be considered a mechanism of HGT, is a continual source of novel influenza viruses and can lead to the emergence of pandemic strains. In the FluMist vaccine strains, the haemagglutinin and neuraminidase segments from contemporary circulating strains replace the equivalent segments from the cold-adapted parent strains. Reassortment could lead to the introduced segments being replaced. The same process could also result in the transfer of the introduced haemagglutinin and neuraminidase segments to a circulating strain. Other genomic segments could also reassort between the vaccine strains and circulating strains.

175. The two influenza A vaccine viruses in the FluMist vaccine reassorted at low levels in vaccine recipients (Buonagurio et al. 2006). The reassortants were attenuated as they always carried six segments from the cold adapted parent.

176. For the CodaVax and other SAVE flu vaccine strains, the haemagglutinin and neuraminidase segments are modified by directed mutagenesis from their parental strains. Reassortment could lead to the introduced genetically modified segments being replaced. The same process could also result in the transfer of the introduced haemagglutinin and neuraminidase segments to a circulating strain. Other genomic segments of the CodaVax and other SAVE flu vaccine strains could also reassort between the vaccine strains and circulating strains.

2.2.1 Risk scenario 9 – GMO and contemporary influenza virus reassortment

Risk source	Causal pathway	Potential harm
GM CodaVax, unspecified SAVE flu vaccines or FluMist vaccines	i. Exposure of people or animals to the GM virus leading to infection (see risk Scenarios 1-8)	Ill health
	↓	
	ii. Person or animal also infected with contemporary influenza virus carrying a different haemagglutinin and/or neuraminidase from the vaccine strains	
	↓	
	iii. Both viruses infect and replicate in the same host cell	
↓		
iv. Reassortment between viral genomes takes place and recombinant virus propagates	↓	
v. Establishment of viral infection.		

Causal pathway

177. For reassortment to occur, two different influenza viruses of the same type must co-infect a host cell. If this does occur, reassortment could theoretically result in viral progeny having any permutation of the genomic segments of the parent viruses.

178. The GM flu vaccine strains would be present when people are vaccinated. The vaccine will only be given to a small number of healthy males. The likelihood of a person being unintentionally infected with the GM flu vaccine strains is extremely low (see Risk scenarios 1 and 2), and the GM flu vaccine strains would generally not be transmitted from vaccinated or otherwise infected people. Animals are not expected to become infected with the GM flu vaccines (see Risk scenario 7). The contemporary strains would only be prevalent during the influenza season, which usually begins in late autumn and peaks in winter, and only a small proportion of the population experience flu infection each year.

Potential harm

179. If FluMist vaccine viruses reassort with a circulating influenza virus, the introduced haemagglutinin and/or neuraminidase segments could transfer from the GM flu vaccine viruses to influenza strains in the environment. However, these segments are derived from strains in circulation, and indeed are chosen as vaccine targets because they are predicted to be the most widely circulating strains for the season. Therefore, such a reassortant would introduce no genetic novelty into the environment and would not alter the epidemiology of the influenza season.

180. Different haemagglutinin and/or neuraminidase segments could also be transferred into the FluMist vaccine viruses by reassortment with a circulating strain other than the target strains. The overwhelming majority of genetically novel reassortants would retain the attenuated phenotype of the vaccine strains, and be less pathogenic than the circulating strain.

181. Theoretically, reassortment can generate any combination of genomic segments from the FluMist vaccine strains and circulating strains but analysis of reassortants shows that not all reassortants occur with equal probability (Angel et al. 2013; Wendel et al. 2015). This may be due to the preferential packaging of some segments, decreased replicative fitness of some reassortants due to mismatches in the haemagglutinin and neuraminidase (see [DIR 137 RARMP](#), Chapter 1, Sections 4.7 and 4.8), or mismatches in other viral components (Treanor & Murphy 2015). Additionally, as noted in Chapter 2 Section 2.2 above, all of the genes and genomic segments in the FluMist vaccines would be derived from existing flu strains, and therefore reassortment would not introduce any novel genetic material.

182. A study of GM flu vaccine viruses in ferrets showed that when an attenuated vaccine virus and a wild-type influenza virus reassort, the likely outcome is viruses that are attenuated or less virulent than wild-type strains (Parks et al. 2007). No reassortant was more virulent than wild-type, and the majority of reassortants replicated less efficiently in infected ferrets. This could be explained by the attenuating mutations of the GM flu vaccine viruses being located on different genomic segments, increasing the likelihood of the presence of attenuating mutations in any reassortant.

183. If CodaVax or other SAVE flu vaccine viruses reassort with a circulating influenza virus, the modified haemagglutinin and/or neuraminidase segments could transfer from the GM flu vaccine virus to influenza strains in the environment. These GM genomic segments were derived from strains in circulation, chosen as vaccine targets because they are predicted to be the most widely circulating strains for the season, and the HA and NA segments genetically modified to attenuate the vaccine strain. Therefore, such a reassortant would introduce genetic novelty into the environment, however the new influenza strains produced would be less virulent or no more virulent than the wild-type circulating strains.

Conclusion

184. Risk Scenario 9 is not identified as a substantive risk. Co-infection of a host cell by the GMOs and another strain would be uncommon, and reassortants would be less or no more virulent than circulating strains. Therefore, this risk would be negligible and does not warrant further detailed assessment.

2.2.2 Risk scenario 10 – GMO and swine/avian influenza virus reassortment

Risk source	Causal pathway	Potential harm
GM CodaVax, unspecified SAVE flu vaccines or FluMist vaccines	i. Trial participant or another person infected with the GMO is infected with an influenza virus of swine or avian origin ↓	Ill health
	ii. Both viruses co-infect the same host cell ↓	
	iii. GMO and swine/avian influenza virus reassort ↓	
	iv. Haemagglutinin and/or neuraminidase segment in GMO is replaced with equivalent segment from swine or avian influenza strain ↓	
	v. Reassortant infects host and recombinant virus propagates ↓	
	vi. Establishment of viral infection	

Causal pathway

185. As noted in Risk scenario 9, for reassortment to occur two different influenza viruses of the same type must co-infect a host cell. The vaccine will only be given to a small number of healthy males. The likelihood of a person being unintentionally infected with the GM flu vaccine strains is extremely low (see Risk scenarios 1 and 2), and the GM flu vaccine strains would generally not be transmitted from vaccinated or otherwise infected people.

186. In addition, exposure of people to influenza viruses of avian or swine origin in Australia is very rare for the following reasons:

- swine influenza viruses are not endemic in Australia and transmission requires close contact with infected swine
- surveillance by the Department of Agriculture and Water Resources indicates the H5N1 avian influenza virus is not present in Australia, and no cases of H7N9 avian influenza have been reported in Australia.
- migratory birds infected with and suffering the symptoms of avian influenza are unlikely to complete the flight to Australia
- while there was an outbreak of H7N2 avian influenza in the municipality of Young NSW in 2013, there have been no reports of avian influenza since then
- the most common mode of transmission for avian influenza viruses is the faecal to oral route and they do not transmit efficiently via the airborne route (de Graaf & Fouchier 2014; Sorrell et al. 2011).

Potential harm

187. Reassortment between the FluMist vaccine strains and influenza strains of avian/swine origin could result in either or both the haemagglutinin and neuraminidase segments in the GM flu vaccine strain being replaced by the equivalent segments from the swine/avian strain. This would alter the antigenic characteristics of the influenza virus but it would remain cold-adapted and attenuated (see DIR 137 RARMP, Chapter 1, Sections 4, and Chapter 2, Section 2.1).

188. A similar reassortment between the CodaVax or SAVE flu vaccine strains and influenza strains of avian/swine origin could result in either or both the haemagglutinin and neuraminidase segments in the GM flu vaccine strain being replaced by the equivalent segments from the swine/avian strain. This would alter the antigenic characteristics of the influenza virus and depending on the reassortment, the virus may or may not be attenuated. In

any case, the reassortments would be the same or less virulent than reassortants between an avian or pig strain and a circulating flu strain.

189. Not all reassortants are viable as a novel haemagglutinin-neuraminidase combination may lack the optimal balance between binding to and release from the receptor that is required for productive infection (see [DIR 137 RARMP](#), Chapter 1, Sections 4.7 and 4.12).

190. If avian flu haemagglutinin replaces the GM flu vaccine strain haemagglutinin, non-optimal cellular tropism could prevent or limit infection. Avian flu haemagglutinin preferentially binds the SA α -2,3 receptor which is present in low quantities in the human nasopharynx and lung (de Graaf & Fouchier 2014). In the nasopharynx, the human SA α -2,3 receptors, being O-linked, would be cleaved poorly by avian flu neuraminidase (see [DIR 137 RARMP](#), Chapter 1, Section 4.12). Virus aggregation would result and this would impede repeated cycles of infection. In the lung, the temperature would restrict replication of the cold-adapted reassortant.

191. Should the above mentioned FluMist reassortants infect swine and avian species, their replication would also be restricted. Some segments in these reassortants would be derived from the cold-adapted parent strain and the proteins encoded by these segments would not be expected to function optimally at the higher body temperatures of these species. The vaccine viruses were unable to productively infect experimentally inoculated pigs or birds (see [DIR 137 RARMP](#), Chapter 1, Section 5.5.3).

192. If avian/swine neuraminidase replaces the GM flu vaccine strain neuraminidase, poor receptor cleavage would restrict replication. The avian/swine neuraminidase preferentially cleaves the SA α -2,3 receptor and it would have to act on a human haemagglutinin which preferentially binds the SA α -2,6 receptor (see [DIR 137 RARMP](#), Chapter 1, Section 4.12). Poor cleavage of this receptor would promote aggregation and restrict replication.

193. The attenuating mutations in the FluMist vaccine strains are located on different genome segments. If a FluMist vaccine strain reassorts with an avian/swine strain, the reassortants are likely to be less virulent than when a circulating human flu strain reassorts with an avian/swine strain.

194. FluMist was in use during the 2009 swine flu pandemic in the USA. This would have provided an opportunity for the GM flu vaccine strains to reassort with the swine flu virus. When similar reassortants were constructed in the laboratory, they were found to be attenuated (Zhou et al. 2012). There was no evidence of any such reassortment with the vaccine leading to new, persistent circulating strains during the pandemic.

195. As noted in Risk scenario 9, although reassortment can generate any combination of segments from the two co-infecting viruses, analysis of reassortants shows that not all reassortants occur with equal probability (Angel et al. 2013; Wendel et al. 2015). This may be due to the preferential packaging of segments, decreased replicative fitness of reassortants due to mismatches in the haemagglutinin and neuraminidase (see [DIR 137 RARMP](#), Chapter 1, Sections 4.7 and 4.12), or mismatches in other viral components. Additionally, as noted in Chapter 2 Section 2.2 above, all of the genes and segments in the FluMist vaccines would be derived from existing flu strains, and therefore reassortment would not introduce any novel genetic material.

Conclusion

196. Scenario 10 is not identified as a substantive risk. Co-infection of a host cell by a GM flu vaccine strain and an avian or pig flu strain would be highly unlikely and reassortants would be no more virulent than reassortants between an avian or pig strain and a circulating flu

strain. Therefore, this risk would be negligible and does not warrant further detailed assessment.

Section 3 Risk characterisation

197. Ten risk scenarios were postulated and evaluated. They are summarised in Table 2, where circumstances that share a number of common features are grouped together in broader risk categories. In the context of control measures proposed by the applicant, two of the risk scenarios were identified as posing substantive risks which warranted further assessment. More detail on the evaluation of these scenarios is provided in this Section.

3.1.1 Risk scenario 6 – Exposure of at-risk people to GM virus due to shedding by trial participants

Risk source	Causal pathway	Potential harm
GM CodaVax and FluMist vaccines	i. Treatment of trial participant with the GMO ↓	Ill health
	ii. Trial participant sheds the GMO ↓	
	iii. Exposure of at-risk people (such as immunocompromised persons; e.g. carers or household contacts, clinical patients) through contact with trial participant or contaminated items (e.g. contaminated tissues/waste) ↓	
	iv. Establishment of viral infection	

Likelihood assessment

198. Trial participants are expected to shed the GM virus for up to one week after administration. Once trial participants return home after treatment, home carers and close contacts (e.g. partners and other family members) could be exposed to the shed GM virus. Participants will return to the clinic daily for 6 days following administration of the GM flu vaccine, for assessment and follow-up testing, potentially exposing other patients. Certain individuals are likely to suffer more severe responses to the GM virus than the general population. Some of the people exposed to the GM viruses shed by trial participants may be such at-risk people.

199. The extent to which trial participants shed the GMO is an important factor in assessing its potential for transmission. In influenza infections, shedding of detectable amounts of influenza virus begins the day before symptoms appear. Viral replication peaks approximately 48 hours after transmission and declines slowly from there. Shedding continues for a further three to five days in adults and up to seven days in young children (Wright et al. 2007). Only healthy adult males will be enrolled in the trial.

200. No human studies on shedding of the CodaVax vaccine virus (or other SAVE flu vaccines) have been performed. In a non-clinical study using ferrets, shedding of the CodaVax vaccine virus occurred up to 4 days after administration and there was no evidence of shedding after 4 days (which was examined for 6 days).

201. For any vaccine virus to transmit from a vaccinated individual to another individual, the amount of virus shed has to be greater than or equal to the infectious dose, indicating human to human transmission is possible but would be highly unlikely for an attenuated virus. The findings of several non-clinical studies on shedding after the administration of LAIVs indicated that shed viral titres were low (Block et al. 2008; Mallory et al. 2011).

202. Those at highest risk include the elderly, young children, pregnant women and the immunocompromised. Influenza generally aggravates respiratory conditions such as asthma. It is possible that at-risk people among a participant's close associates or other patients in the clinic could be exposed to the GM virus before the participant is aware that they should avoid contact with that person.

203. The applicant has proposed a number of controls to limit exposure to the GM flu vaccines, and to restrict its spread and persistence in the environment. These controls include excluding prospective participants with pet birds and those with a known immune deficiency. All trial participants will be required to follow well-established hygiene practices known to minimise interpersonal transmission of the flu virus. These practices will be explained to prospective participants during initial screening, and anyone unwilling or unable to comply will not be enrolled in the trial.

204. Trial participants will be instructed to use tissues to collect any respiratory secretions as a result of sneezing, coughing or eye secretions for seven days after administration of the GM flu vaccine. Trial participants will be instructed to place the tissues into small sealable bags, which in turn are to be placed within biohazard containers provided by the applicant. The biohazard containers with the bags of used tissues are to be returned to the study site at the participants next scheduled visit, for disposal in the clinical waste stream. This practice would minimise exposure of potential contacts.

205. These measures are, in part, consistent with the recommendations for routine use of vaccines in children, adolescents, and adults developed by the United States Center for Disease Control and Prevention (US CDC) Advisory Committee on Immunization Practices (ACIP) for LAIVs (FluMist) (Grohskopf et al. 2015). These measures would limit the opportunity for persons to come into contact with the GM virus.

206. This scenario is considered **unlikely** to occur because: the GM flu vaccines are attenuated; the length of time flu virus shedding occurs is limited; shedding titres of the GM flu vaccines viruses would be low; trial participants would follow established hygiene practices. These factors minimise the likelihood that an at-risk person would be exposed to the GM virus in a manner that leads to infection.

Consequence assessment

207. The effect of the GM virus on at-risk individuals is unknown, as exposure of such individuals has not been reported. As the genetic modifications attenuate the flu viruses, the consequences of infection are expected to be less severe than for infection with circulating strains of influenza. The consequences of exposure to the GM flu vaccine viruses must be viewed against the background prevalence of flu in the population.

208. Given the uncertainty regarding the ability of the GMO to induce an adverse reaction in at-risk people, the potential harm to this group may therefore be considered **marginal** (minimal or no increase in illness/injury to people) to **minor** (minor increase in illness/injury to people that is readily treatable).

Risk estimate

209. The risk estimate is based on a combination of the likelihood and consequence assessments, using the Risk Estimate Matrix (see Chapter 2, Section 1), as described in the Regulator's Risk Analysis Framework (OGTR 2013).

210. The consequences of exposure leading to infection via this pathway are considered **marginal to minor** but **unlikely** to occur. The risk is therefore estimated to be **negligible** (risk is of no discernible concern and there is no present need to invoke actions for mitigation) to

low (risk is of minimal concern, but may invoke actions for mitigation beyond standard practices). Consideration of the need for treatment of this low risk is made in Section 5, below.

3.1.2 Risk scenario 8 – Direct or indirect exposure to unspecified GM SAVE flu vaccines.

Risk source	Causal pathway	Potential harm
Unspecified GM Save flu vaccines	i. Risk scenarios 1-7 as described above	Ill health

Likelihood assessment

211. The proposed study includes randomized active and placebo-controlled clinical trials, with a number of SAVE flu vaccines. In the application, the CodaVax vaccine parental strain is identified and evidence relating to the attenuation of the CodaVax vaccine *in vitro* and *in vivo* has been provided. The proposed study also includes a number of as yet unspecified SAVE flu vaccines, where the parental flu strains is not identified and no evidence relating to the attenuation of the unspecified SAVE flu vaccines, either *in vitro* or *in vivo*, has been provided.

212. The causal pathway for unspecified SAVE flu vaccines includes all pathways identified and described in Risk scenarios 1-7 in Chapter 2 but with the risk source being the unspecified SAVE flu vaccines.

213. There have been a number of studies examining the strategy of codon deoptimisation for virus attenuation (see Chapter 1, Section 5.2.2). Currently, there is one published study that demonstrates viral attenuation of influenza (strain A/Puerto Rico/8/34 (H1N1)) by codon deoptimisation of the HA and NA genomic segments (Yang et al. 2013). This application has also provided *in vitro* and *in vivo* data for CodaVax to support the theory that codon deoptimisation of HA and NA genomic segments in influenza results in attenuation of the virus.

214. The SAVE strategy for codon deoptimisation of influenza HA and NA genomic segments outlined in this application relies on unique genetic mutations for each individual influenza strain. In the FluMist vaccine strains, the HA and NA genomic segments in a cold-adapted parent virus are replaced by the equivalent segments from a strain to be targeted by the vaccine (see [DIR 137 RARMP](#), Chapter 1, Section 5.3).

215. For flu vaccines based on the SAVE strategy, there is expected to be variability in relation to the level of attenuation as a result of unique genetic mutations to each individual influenza strain. It is possible that one or more of the unspecified SAVE flu vaccine strains may not be sufficiently attenuated for consideration as a vaccine strain. If a SAVE flu vaccine strain is not sufficiently attenuated, it may be shed in larger amounts and therefore more likely to lead to infection of other people and persistence in the environment. The SAVE codon deoptimisation strategy has resulted in attenuation of two influenza strains – based on the Yang et al. 2013 study and CodaVax, the SAVE strategy should result in attenuation of the unspecified SAVE flu vaccines. Only a small number of healthy adult males will be enrolled in the trial (up to 500 over a 5 year period), limiting the potential level of exposure.

216. Overall, this scenario is considered **unlikely** to occur.

Consequence assessment

217. The effect of the unspecified SAVE flu vaccines on people or animals is unknown and at the moment, purely theoretical. The consequences of infection by unspecified SAVE flu vaccines may or may not be less severe than those described for unmodified influenza.

However, the SAVE flu vaccines are not expected to produce more severe infection than unmodified circulating flu viruses. These vaccine strains will encode HA and NA proteins identical to those of their parental (target) strain, which will be a strain in circulation at the time, and other genome segments will be identical to those of the parental strain. Thus these vaccine strains will not add any antigenic variation to the pool of circulating flu viruses. The consequences of exposure to the GM flu vaccine viruses must be viewed against this background of flu in the population.

218. Given the uncertainty regarding the ability of unspecified SAVE flu vaccines to induce an adverse reaction in people or animals, the potential harm may be considered **marginal** (minimal or no increase in illness/injury to people) to **minor** (minor increase in illness/injury to people that is readily treatable).

Risk estimate

219. The risk estimate is based on a combination of the likelihood and consequence assessments, using the Risk Estimate Matrix (see Chapter 2, Section 1), as described in the Regulator's Risk Analysis Framework (OGTR 2013).

220. The consequences of exposure via this pathway and infection with the GMO are considered **marginal** to **minor** but **unlikely** to occur. The risk is therefore estimated to be **negligible** (risk is of no discernible concern and there is no present need to invoke actions for mitigation) to **low** (risk is of minimal concern, but may invoke actions for mitigation beyond standard practices). Consideration of the need for treatment of this moderate risk is made in Section 5, below.

Section 4 Uncertainty

221. Uncertainty is an intrinsic part of risk analysis⁵. There can be uncertainty about identifying the risk source, the causal linkage to harm, the type and degree of harm, the chance of harm occurring or the level of risk. In relation to risk management, there can be uncertainty about the effectiveness, efficiency and practicality of controls.

222. For clinical trials, which involve research, some knowledge gaps are inevitable. This is one reason they are conducted under specific limits and controls intended to minimise exposure to the GMO and thus decrease the likelihood of harm.

223. For DIR 144, uncertainty is noted particularly in relation to the degree of attenuation of the SAVE flu vaccines relative to unmodified influenza, and its likely effect on people.

224. There is limited data comparing the GM CodaVax vaccine strain with the parent organism, and no data on other unspecified SAVE flu vaccines, on which to base a robust assessment of their attenuation and safety. In contrast there is significant overseas experience with the active comparator vaccine, FluMist (see Section 7.2).

225. The uncertainty about the ability of the CodaVax to cause adverse reactions in at-risk people has been taken into account in Risk scenario 6. Consideration of this uncertainty in the consequence assessment resulted in the estimate of risk of negligible to low.

226. Although Risk scenario 8 considered information about the unmodified influenza virus, as well as about CodaVax and another GM flu strains with similar genetic modifications, uncertainty remains relating to the degree of attenuation of other as yet unspecified SAVE flu vaccines and possible effects in people. Consideration of this uncertainty in the consequence assessment resulted in the estimate of risk of negligible to low for Risk scenario 8.

⁵ A more detailed discussion is contained in the Regulator's *Risk Analysis Framework* available from the [OGTR website](#) or via Free call 1800 181 030.

Section 5 Risk Evaluation

227. 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 whether additional information is needed.

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

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

229. Ten risk scenarios were postulated whereby the proposed dealings could give rise to harm to people or the environment. This included consideration of the potential for: the genetic modifications to impact on the characteristics of the GM flu viruses; infection of people, including at-risk individuals; and infection of animals. The opportunity for gene transfer to other organisms, and its effects if it were to occur, was also considered.

230. 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 ten risk scenarios was identified as a substantive risk requiring further assessment.

231. The likelihood and consequences of the identified substantive risks were characterised (Chapter 2, Section 3), and the level of risk estimated using the Risk Estimate Matrix, as described in the Regulator's Risk Analysis Framework (OGTR 2013) (see Chapter 2, Section 1).

232. The risk from exposure of at-risk individuals through contact with trial participants who are shedding the CodaVax or FluMist vaccine strains was estimated as posing negligible to low risks to human health and safety. The effect of the other as yet unspecified SAVE flu vaccines on people or animals as a result of GM virus exposure was estimated as posing negligible to low risks to health and safety to humans and animals.

233. The applicant has proposed some control measures related to these risks. Additional treatment measures to mitigate each of the identified negligible to low risks should be applied. Treatment measures to manage these risks are considered in Chapter 3.

234. Given that the two substantive risks are assessed as negligible to low, the Regulator considers that the dealings involved in this proposed release do not pose a significant risk to either people or the environment.

Chapter 3 Risk management

Section 1 Background

235. 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, evaluates controls and limits proposed by the applicant, and considers general risk management measures. The risk management plan informs the Regulator's decision-making process and is given effect through licence conditions.

236. 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.

237. 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.

238. 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 and to manage risk to people or the environment. In addition, the Regulator has extensive powers to monitor compliance with licence conditions under section 152 of the Act.

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

Section 2 Risk treatment measures for substantive risks evaluated as requiring treatment

240. The risk identification process (Chapter 2 Section 2) led to identification of two substantive risks. These risks, relating to exposure of at-risk individuals to GM virus shed by trial participants and exposure of people and animals to unspecified SAVE flu vaccines, were characterised in Chapter 2, Section 3. Risk evaluation proposed that these risks should be treated.

241. The applicant has proposed that trial participants follow well-established hygiene practices to minimise interpersonal transmission. The applicant has not proposed measures to limit contact with at-risk individuals as outlined by the US CDC ACIP for GM LAIVs (FluMist) (Grohskopf et al. 2015). The risk posed by transmission to at-risk individuals from trial participants shedding the GM virus was assessed as negligible to low. To manage this risk, the licence holder could instruct all trial participants not to care for severely immunosuppressed persons who require a protective environment and avoid contact with such persons for 7 days after administration of the GM flu vaccines, as outlined by the US CDC ACIP (Grohskopf et al. 2015). The treatment measure is considered to be practical and a requirement for trial participants to be informed of this measure and excluded from the trial if unwilling or unable to comply has been included as a licence condition.

242. The risk posed by exposure of people and animals to unspecified SAVE flu vaccines was assessed as negligible to low, due to the uncertainty about the attenuation and possible effects of these uncharacterised GM flu strains.

243. To manage this risk, the unspecified SAVE flu vaccine strains proposed in the application are not included in the licence. This treatment measure is considered to be practical and effective. However if, during the term of the licence, the licence holder was to generate data on the characterisation of additional SAVE flu strain vaccine strains, the Regulator could consider varying the licence to include new strains. At a minimum, similar information to that provided for CodaVax would be needed, such as:

- identification of parental influenza strains for each SAVE flu vaccine
- details of genetic modifications
- characterisation of the GM HA and NA genomic segment nucleotide sequences
- evidence of genetic stability in cell line(s) used for manufacturing
- evidence of attenuation through appropriate *in vitro* cell line experiments
- evidence attenuation and safety as demonstrated by appropriate *in vivo* ferret studies.

2.1 Summary of licence conditions to manage identified risks

244. Licence conditions have been imposed to reduce the potential for transmission of the GMOs from trial participants to at-risk individuals, and to ensure that each SAVE flu vaccine included in the clinical trials has an attenuated phenotype. These include requirements that:

- all trial participants be instructed not to care for severely immunosuppressed persons who require a protective environment and avoid contact with such persons for 7 days after treatment
- prior to each new GM strain being included in the trial, the licence holder must provide details of genetic modifications and non-clinical *in vivo* and *in vitro* evidence for the attenuation of each individual SAVE flu vaccine strain, and receive approval from the Regulator by way of a variation to the licence.

Section 3 General risk management

245. The limits and controls proposed in the application were important in establishing the context for the risk assessment and in reaching the conclusion about the risks posed to people and the environment. Therefore, to maintain the risk context, licence conditions have been imposed to limit the release in scale and duration, and to restrict the spread and persistence of the GMOs and their genetic material in the environment.

3.1 Consideration of the limits and controls proposed by Clinical Network Services (CNS) Pty Ltd

246. Chapter 1, Sections 3.2 and 3.3 provide details of the limits and controls proposed by CNS, which are discussed in the risk scenarios considered in Chapter 2. The appropriateness of these limits and controls is considered further below.

247. The proposed clinical trials will involve a maximum of 500 participants within Australia, and most activities will take place in clinical trial units, hospitals and laboratory facilities. Activities that will happen outside the CROs include transport, disposal of GM flu vaccines and trial participants living outside of the CRO during the clinical trials. The GM flu vaccines strains will depend on WHO and AIVC advice on the antigen composition of flu vaccines for the current or upcoming flu season for the southern hemisphere. The applicant has proposed to complete the trial within five years of commencement. These limits would restrict the flu strains used in the study and minimise the exposure of people and animals to the GM viruses.

248. Import and transport will be in accordance with relevant International Air Transport Association requirements and/or the Regulator's guidelines. Once at the pharmacy or final destination in the clinical facility, the GM flu vaccines will be stored in a secure location with access limited to the site pharmacist and medical staff according to the *National vaccine storage guidelines: Strive for 5, 2nd Edition* (Department of Health and Ageing 2013) and the *Standard for the Uniform Scheduling of Medicines and Poisons* (Therapeutic Goods Administration 2016). These conditions will minimise potential for exposure of people and the environment to the GM flu vaccines and have been included in the licence conditions.

249. The trial participants are limited to healthy adult males and proposed exclusion criteria are outlined in Chapter 1, Section 3.1.2. These criteria include excluding prospective participants with a known immune deficiency. The inclusion and exclusion criteria for trial participants will be subject to approval by a HREC, who will consider the safety of the individuals involved in the trial. This will also serve to minimise the potential for spread and persistence of the GM viruses. All clinical trial staff will be required to have an influenza vaccination one month prior to handling GM flu vaccines. These measures have been included in licence conditions.

250. Participants will be inoculated by nasal administration of the GM flu vaccines by trained clinical staff at clinical facilities according to the clinical protocol and in accordance with ICH-GCP (ICH 1996), the TGA Good Clinical Practice guidelines (Therapeutic Goods Administration 2000) and Australian Guidelines for the Prevention and Control of Infection in Healthcare (National Health and Medical Research Council 2010). These practices would minimise exposure of people handling and administering the GM flu vaccines and has been included in licence conditions.

251. Clinical staff dispensing concentrated GM flu vaccines will work in a biological safety cabinet (BSC), wear gloves and use personal protective equipment (PPE) as appropriate based on risk assessment. The use of gloves and protective clothing while handling concentrated virus, plus the use of a BSC minimise the likelihood of exposure. As unmodified influenza is classified as a Risk Group 2 organism in Australia, all dispensing of the concentrated the GM flu vaccines should be carried out in a Class II BSC and follow PC2 work practices. These practices would further reduce the potential for exposure of people handling the concentrated GM flu vaccines, and have been included as licence conditions.

252. The applicant will require trial participants to take precautions intended to minimise interpersonal spread of the GMO's, which would reduce the opportunity for exposure of other people to the GMO or shedding of the GMO into the environment. This will include instructing trial participants to use tissues to collect any respiratory secretions as a result of sneezing, coughing or eye secretions for seven days after administration of the GM flu vaccine, and to place the tissues in a sealed bag within in a biohazard container supplied by the applicant, to be returned to the study site for disposal at the participant's next scheduled visit. The applicant will exclude people from the trial if they are unwilling or unable to comply with these precautions. These practices would minimise exposure of household contacts (both human and animal), people and the environment to GM virus shed by the trial participants. Licence conditions have been included to require the licence holder to: educate trial participants about the potential for transmission of the GMO to other people or animals; instruct trial participants in precautions to minimise spread of the GMO; and exclude people from the trial if they are unwilling or unable to comply with these precautions.

253. All waste generated at the clinical sites, or returned by trial participants, will be disposed of in accordance with standard clinical waste disposal practices. This would also minimise exposure of people and the environment to the GMO's and has been included as a licence condition.

254. Maintaining records of all GMO's received, dispensed and destroyed will ensure all vials of the GMO's are accounted for. Destroying all GMO's remaining when the study at clinical sites is complete will ensure it is not inadvertently released at a later time. These practices have been included as licence conditions.

3.1.1 Summary of licence conditions proposed to limit and control the release

255. A number of licence conditions have been imposed to limit and control the proposed release based on the considerations discussed in subsection 3.1 above. These include requirements that:

- limit the release to a maximum of 500 trial participants inoculated with the GM viruses at designated clinical facilities over a 5 year period;
- restrict the method of administration of the GM fluvaccines to nasal administration by dropper or aerosol sprayer;
- exclude immunocompromised people from participation in the trial, to minimise the potential for spread of the GMOs;
- all trial participants be instructed not to care for severely immunosuppressed individuals who require a protective environment and avoid contact with such persons for 7 days after administration of the GMO;
- all dispensing of concentrated GM flu vaccines are to be carried out in a Class II BSC and follow PC2 work practices;
- the GMOs be administered, and trial participants cared for, by trained staff at clinical facilities in accordance with NHMRC Guidelines for the Prevention and Control of Infection in Healthcare, ICH-GCP and TGA GCP guidelines, and that appropriate personal protective equipment is worn and used;
- require that patients be educated about the potential for transmission of the GMO's and instructed in precautions to minimise the spread of GM virus to other people and animals;
- transport and store all GM flu vaccines in accordance with relevant regulations and guidelines⁶;
- dispose of all waste generated at clinical sites and returned to the clinical sites by trial participants in accordance with standard disposal practices for infectious clinical waste; and
- destroy or return all unused GMO on completion of the study, and maintain records of all GMO received, dispensed and destroyed.

3.2 Other risk management considerations

256. 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;
- identification of the persons or classes of persons covered by the licence;
- reporting structures, including a requirement to inform the Regulator is the applicant becomes aware of any additional information about risks to the health and safety of people or the environment; and
- a requirement that the applicant allow access to the trial sites by the Regulator, or persons authorised by the Regulator, for purpose of monitoring or auditing.

⁶ The Gene Technology Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*; IATA Transportation Regulations

3.2.1 Applicant suitability

257. 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 (both individuals and the body corporate)
- 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.

258. The Regulator considered the suitability of the applicant when the application was received. The Regulator will reassess the suitability of CNS before making the decision whether or not to issue a licence for this application (DIR 144).

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

260. In addition, any applicant organisation must have access to a properly constituted Institutional Biosafety Committee and be an accredited organisation under the Act.

3.2.2 Contingency plans

261. If a licence is issued, the licence holder would be required to submit a contingency plan to the Regulator prior to conducting any dealings authorised by the licence. This plan must detail measures to be undertaken in the event of:

- a) the unintended release of the GMO, including spills outside of clinical sites, and exposure of or transmission to persons other than trial participants; and
- b) a person exposed to the GMO developing a severe adverse response.

262. The licence holder would also be required to provide a method to the Regulator for the reliable detection of the presence of the GMOs and the introduced genetic materials in a recipient organism. This would be required for each GMO prior to conducting dealings with that GMO under the licence.

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

263. If a licence were to be 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. Prior to commencing dealings at any clinical site, CNS would also be required to notify the Regulator of the participating organisation, and provide a list of people who will be covered, or their functions or position where names are not known at the time.

3.2.4 Reporting requirements

264. If issued, the licence would oblige 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 trial
- any contraventions of the licence by persons covered by the licence
- any unintended effects of the trial

265. The licence holder would also be obliged to submit an Annual Report within 90 days of the anniversary of the licence containing any information required by the licence, including

numbers of trial participants inoculated with the GMOs and details of any serious adverse events.

3.2.5 Monitoring for Compliance

266. 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.

267. 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.

268. 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 health and safety of people or the environment could result.

Section 4 Conclusions of the RARMP

269. The risk assessment concludes that the proposed limited and controlled release of GM flu viruses to take place in Australian clinical facilities, involving up to a total of 500 trial participants and expected to run for up to five years, poses negligible to low risks to the health and safety of people or the environment as a result of gene technology.

270. The risk management plan concludes that the identified negligible to low risks can be managed so as to protect the health and safety of people and the environment by imposing licence conditions. Licence conditions are imposed to limit the release in size, locations and duration and to restrict the spread and persistence of the GMO and its genetic material in the environment, as these were important considerations in establishing the context for assessing the risks. Specific risk treatment measures have also been imposed to manage the identified negligible to low risks.

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Appendix A: Summary of submissions from prescribed experts, agencies and authorities⁷

Advice received by the Regulator from prescribed experts, agencies and authorities on the consultation RARMP is summarised below. All issues raised in submissions that related to risks to the health and safety of people and the environment were considered in the context of the currently available scientific evidence and were used in finalising the RARMP that informed the Regulator's decision to issue the licence.

Sub. No.	Summary of issues raised	Consideration in RARMP	Comment
1	Agreed with the overall conclusions of the RARMP.	-	Noted
	The novel GM vaccines are likely to be attenuated. However, requesting additional data on attenuation for unspecified vaccines is warranted considering the trial is first in human.	Chapter 3	Noted
	Further consideration should be given to potential transmission in ferrets to inform safety in humans.	Chapter 2, Section 2, Risk Scenario 6	The potential of the GM CodaVax vaccine to be spread and contribute to disease has been evaluated in detail. The RARMP concludes that the risk is negligible, with the exception of exposure of at-risk individuals (see Risk Scenario 6). In the GM CodaVax and other SAVE vaccine strains, the HA and NA segments of the parent virus will be modified by incorporating a large number of mutations which do not change the encoded amino acid (protein) sequences. Therefore the GM vaccine strains will have the same antigenic makeup as the unmodified parent flu strains. Exposure would be minimal as the GM CodaVax vaccine is attenuated compared to naturally occurring influenza virus (which is widespread in the Australian environment), having reduced ability to replicate and decreased potential for transmission or persistence. Consequences of exposure to the GM CodaVax vaccine would also be minimised for the same reasons.
	Further consideration should be given to potential risks to pregnant women as a result of potential shedding of vaccine virus.	Chapter 2, Section 2, Section 3.1.1, Risk scenario 6; Chapter 3, Section 2	The risk posed by transmission to at-risk individuals from trial participants shedding the GM virus was assessed as negligible to low (see Risk Scenario 6). The US CDC ACIP for GM live attenuated influenza vaccines (FluMist) recommends that GM live attenuated influenza vaccines not be administered to certain at-risk individuals, including pregnant women, but does not indicate that vaccinated individuals should avoid contact with such people. Exposure would be minimal as the GM vaccines are attenuated compared to naturally occurring influenza virus (which is widespread in the Australian environment), having reduced ability to replicate and decreased potential for transmission or persistence.

⁷ Prescribed agencies include GTTAC, State and Territory Governments, relevant local governments, Australian Government agencies and the Minister for the Environment.

Sub. No.	Summary of issues raised	Consideration in RARMP	Comment
2	Agreed with the conclusions of the RARMP that the risk to the environment is negligible.	-	Noted
	Further consideration to influenza virus anthroponosis in relation to Australian native animals.	Chapter 1, Section 6.4 Chapter 2 Section 2.1.3, Risk scenario 3 and Section 2.1.7, Risk scenario 7	Further information relating to the ability of unmodified <i>influenza virus</i> to undergo zoonosis or anthroponosis has been added to Chapter 1 of the RARMP. The potential of the GM virus to spread to animals was considered. The GM flu vaccines are attenuated compared to the parent viruses (which are widespread in the Australian environment), and would not be expected to replicate to high titres in humans, minimising the likelihood of transmission to Australian native animals. Additional detail has been included in Risk scenario 3 of the RARMP.
	Further consideration of the possibility that novel nucleotide sequences could increase virulence in Australian native animals.	Chapter 1, Section 5.2.2, Section 6.4 Chapter 2, Section 2.1.3, Risk scenario 3	The amino acid sequences of the viral proteins of the GM SAVE vaccines will remain unchanged and therefore the SAVE vaccines will have the same tropism as wild type influenza virus. The silent mutations in the GM SAVE vaccines are designed in relation to human hosts. Codon and codon pair preferences are highly conserved across mammalian species and CodaVax has shown to be attenuated in mammals (mice and ferrets). Given this and the large number of codons that have been deoptimised, it is expected that the attenuated phenotype of the GM virus would be retained for any animal species susceptible to human influenza. Therefore it is highly unlikely that the GM SAVE vaccines would have an increase in virulence in Australian native animals susceptible to human influenza anthroponosis. Additional detail has been included in Risk scenario 3 of the RARMP.
	Considers the limits and controls of the clinical trial, together with the attenuation of the GM virus in humans, will reduce the potential for transmission to non-human hosts.	-	Noted.
3	Supported the conclusion of the RARMP that the proposed dealings pose negligible risk of harm to human health and the environment.	-	Noted.
	Considers making codon changes to flu haemagglutinin (HA) and neuraminidase (NA) to be risky, as HA and NA are believed to be key in creating potentially dangerous influenza viruses.	Chapter 1, Section 5.2 Chapter 2, Section 3, Risk scenario 8	It is changes to the amino acid sequence of flu virus HA or NA proteins that have the potential to alter the antigenicity and virulence of the flu virus, (see DIR 137 RARMP, Chapter 1, Section 4.8). In the GM CodaVax and other SAVE vaccine strains, the HA and NA segments of the parent virus will be modified by incorporating a large number of mutations which don't change the encoded amino acid (protein) sequences. Therefore the GM strains will have the same antigenic makeup as the unmodified parent strains.

Sub. No.	Summary of issues raised	Consideration in RARMP	Comment
	Suggests that it would be prudent to get a greater knowledge of, and more experience with, effects of codon deoptimisation in other viruses before it is applied to flu vaccines in people.	Chapter 3, Section 2 and Section 3	The RARMP for this application concludes that the proposed trial of GM flu viruses poses negligible to low risks to the health and safety of people or the environment. Specific risk treatment measures have been imposed to manage these risks, including not authorising the as yet uncharacterised SAVE vaccine strains in the licence, and educating trial participants about methods to minimise transmission of the GMOs. Licence conditions have also been imposed to limit the release in size, locations and duration, as these were important considerations in establishing the context for assessing the risks.
	Risk related to transmission of SAVE flu vaccines to animals is difficult to quantify.	Chapter 1, Section 6.4 Chapter 2, Risk scenario 7	Further information relating to the ability of unmodified <i>influenza virus</i> to undergo zoonosis or anthroponosis has been added to Chapter 1 of the RARMP. The potential of the GM virus to spread to animals was considered. The GM flu vaccines are attenuated compared to the parent viruses (which are widespread in the Australian environment), and would not be expected to replicate to high titres in humans, minimising the likelihood of transmission to animals.
	There were no safety studies reported in immunodeficient animal models such as severe combined immunodeficiency (SCID) mice. Consideration should be given to conducting such studies prior to larger-scale efficacy studies.	Chapter 1, Section 5.2.2 Chapter 2 Chapter 3	The application included <i>in vivo</i> pathogenicity, protective immunity and safety studies with the GM CodaVax vaccine in mice and/or ferrets, with ferrets being the preferred animal model for influenza testing. This information is considered in the RARMP. Risks to people and the environment were assessed as negligible to low. The Regulator has imposed licence conditions to manage the risks by minimising potential for transmission, particularly to severely immunocompromised people, and to ensure that there is ongoing oversight of the release, including an obligation to report any unintended effects.
	Recommend the exclusion criteria include participants living with immunocompromised individuals (household contacts) in whom live attenuated vaccines are normally contraindicated (as per the immunisation handbook) and infants less than 6 months of age who are too young to be immunised with influenza vaccine.	Chapter 2, Section 2, Section 3.1.1, Risk scenario 6; Chapter 3, Section 2	The risk posed by transmission to at-risk individuals was assessed as negligible to low (see Risk Scenario 6). To manage this risk, the licence holder is to instruct all trial participants not to care for severely immunosuppressed persons, as recommended by the US CDC ACIP) for GM live attenuated influenza vaccines (FluMist) (Grohskopf et al. 2015). The USA CDC ACIP recommends that GM live attenuated influenza vaccines not be administered to certain individuals, including pregnant women, but does not indicate that vaccinated individuals should avoid contact with such people.
	Other household contacts such as those with diabetes or cardiorespiratory diseases or pregnant mothers should be less worried about as they are immunocompetent and should be immunised with the seasonal influenza vaccine.	-	Noted.
	The trial staff looking after the participant would be at negligible risk for transmission of the virus as they can take relevant precautions.	-	Noted

Sub. No.	Summary of issues raised	Consideration in RARMP	Comment
	There are no concerns about the comparator vaccine FluMist that has an established safety profile	-	Noted.
	Will future testing of this product include people who are currently excluded?	Chapter 1, Section 2.1 Chapter 3	The Therapeutic Goods Administration (as the primary regulatory agency), the trial sponsor, the investigators and the Human Research Ethics Committee (HREC) at each trial site all have roles in ensuring trial participants' safety under the <i>Therapeutic Goods (Therapeutic Goods Administration 2000) Act 1989</i> . Therefore, the Regulator's assessment focuses primarily on risks posed to people other than those participating in the clinical trial, and to the environment. However, the licence only permits inoculation of healthy adult males, and any proposal to include other people would require a further application to and assessment by the Regulator.
	How will the vaccine effect asthmatics and what precautions should participants take apart from avoiding contact with associates?	Chapter 2 Chapter 3	This will be the first human clinical study to assess the safety and tolerability of a new GM flu vaccine, CodaVax. Currently there is no information on the effect of the CodaVax in asthmatics. The Regulator has imposed licence conditions to minimise the potential for transmission and ensure that there is ongoing oversight of the release, including an obligation to report any unintended effects.

Appendix B: Summary of submissions from the public on the consultation RARMP

The Regulator received one submission from the public on the consultation RARMP. The issues raised in this submission are summarised in the table below. All issues raised in the submission that related to risks to the health and safety of people and the environment were considered in the context of currently available scientific evidence in finalising the RARMP that formed the basis of the Regulator's decision to issue the licence.

Summary of issues raised	Consideration in RARMP	Comment
Concerns related to transmission of live GM flu virus to the general population.	Chapter 1, Section 5; Chapter 2, Sections 2 and 3	<p>The potential of the GM flu vaccines to be spread and contribute to disease has been evaluated in detail in the RARMP. The RARMP concludes that the risk is negligible to low. The GM flu vaccines are significantly attenuated compared to naturally occurring influenza virus and therefore have decreased potential for transmission. Licence conditions have been imposed to manage the identified risks and to limit the release in scale and duration. These conditions include, but are not limited to:</p> <ul style="list-style-type: none"> • exclusion of as yet uncharacterised GM vaccine strains from the trial • requiring that trial participants be instructed to follow well-established hygiene practices that minimise interpersonal transmission • trial participants be instructed not to care for and to avoid contact with severely immunosuppressed individuals.