Australian Government
Department of Health
Office of the Gene Technology Regulator

16 July 2018

Risk Assessment and Risk Management Plan

for

DIR 161

A genetically modified respiratory syncytial virus (RSV) vaccine for use in clinical trials

Applicant – Clinical Network Services (CNS) Pty Ltd

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Summary of the Risk Assessment and Risk Management Plan

for

Licence Application No. DIR 161

Decision

The Gene Technology Regulator (the Regulator) has decided to issue a licence for this application to conduct clinical trials using a genetically modified organism (GMO). It qualifies as a limited and controlled release application under the *Gene Technology Act 2000* (the Act).

A Risk Assessment and Risk Management Plan (RARMP) for this application was prepared by the Regulator in accordance with the requirements of the Act and corresponding state and territory legislation, and finalised following consultation with a wide range of experts, agencies and authorities, and the public. The RARMP concludes that the clinical trials pose negligible risks to human health and safety and the environment and that any risks posed by the dealings can be managed by imposing conditions on the release.

The application

Application number:	DIR 161
Applicant:	Clinical Network Services (CNS) Pty Ltd
Project title:	A genetically modified respiratory syncytial virus (RSV) vaccine for use in clinical trials
Parent organism:	Respiratory syncytial virus
Modified genes and resulting modified trait:	L, N, P, M2-1 and SH genes of RSV (viral attenuation)
Proposed duration:	5 years
Proposed locations:	Clinical trial sites in Melbourne, Sydney, Brisbane, Adelaide and/or Perth
Proposed trial size:	Up to 350 adults of both genders
Primary purpose:	To conduct clinical trials assessing the safety, tolerability and efficacy of a genetically modified (GM) RSV vaccine.

RSV is a common respiratory virus that usually causes mild, cold-like symptoms in adults and older healthy children, but is the most common cause of bronchiolitis and pneumonia among infants and younger children. While people of all ages can be infected, those at highest risk include premature infants, young children, the elderly and people who are immunocompromised. There are currently no available vaccines against RSV. The GM vaccine will be manufactured in the USA and imported into Australia. It will be administered by intranasal spray to up to 350 healthy adult volunteers at specialised clinical facilities located in Melbourne, Sydney, Brisbane, Adelaide and/or Perth. Blood and urine samples for analysis will be collected from trial participants over the course of the study.

Risk assessment

The risk assessment concludes that risks to the health and safety of people, or the environment, from the proposed release are negligible. No specific risk treatment measures are required to manage these negligible risks.

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

Credible pathways to potential harm that were considered included exposure of people or animals to the GMO, potential for persistence of the GMO and the potential for recombination with other viruses. Potential harms that were considered in relation to these pathways included severe RSV disease and increased disease burden in people.

The principal reasons for the conclusion of negligible risks are the attenuated phenotype of the GMO in terms of reduced ability to replicate *in vivo*, the limited host range of RSV, and suitability of the controls proposed by the applicant.

Risk management plan

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

As the level of risk is considered negligible, specific risk treatment is not required. However, since this is a limited and controlled release, the licence includes limits on the size, location and duration of the release, as well as controls to minimise the potential for the GMO to spread in the environment. In addition, there are several general conditions relating to ongoing licence holder suitability, auditing and monitoring, and reporting requirements which include an obligation to report any unintended effects.

Table of Contents

Abbreviations

Act	*Gene Technology Act 2000*
BSC	Biosafety cabinet
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
F	RSV surface fusion glycoprotein gene or protein of RSV
FSANZ	Food Standards Australia New Zealand
G	RSV surface attachment glycoprotein gene or protein of RSV
GM	genetically modified
GMO	genetically modified organism
HREC	Human Research Ethics Committee
IATA	International Air Transport Association
ICH-GCP	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – Guidelines for Good Clinical Practice
L	RSV RNA-dependent RNA polymerase gene or protein of RSV
M	RSV matrix gene or protein of RSV
M2	RSV second matrix gene or protein of RSV
mL	millilitres
mRNA	messenger ribonucleic acid
N	RSV nucleocapsid gene or protein of RSV
NHMRC	National Health and Medical Research Council
NPAAC	National Pathology Accreditation Advisory Council
NS	RSV non-structural gene or protein of RSV
OGTR	Office of the Gene Technology Regulator
ORF	Open reading frame
P	RSV phosphoprotein gene or protein of RSV
PC2	Physical Containment level 2
pfu	plaque forming unit
PIICF	Participant Information and Informed Consent Form
PPE	personal protective equipment
RARMP	Risk Assessment and Risk Management Plan
Regulations	Gene Technology Regulations 2001
Regulator	Gene Technology Regulator
RNA	ribonucleic acid
RSV	*Respiratory syncytial virus*

SH	RSV small hydrophobic gene or protein of RSV
$TCID_{50}$	tissue culture infectious dose 50%
TGA	Therapeutic Goods Administration
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 a licence to conduct 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 in States and Territories, 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).

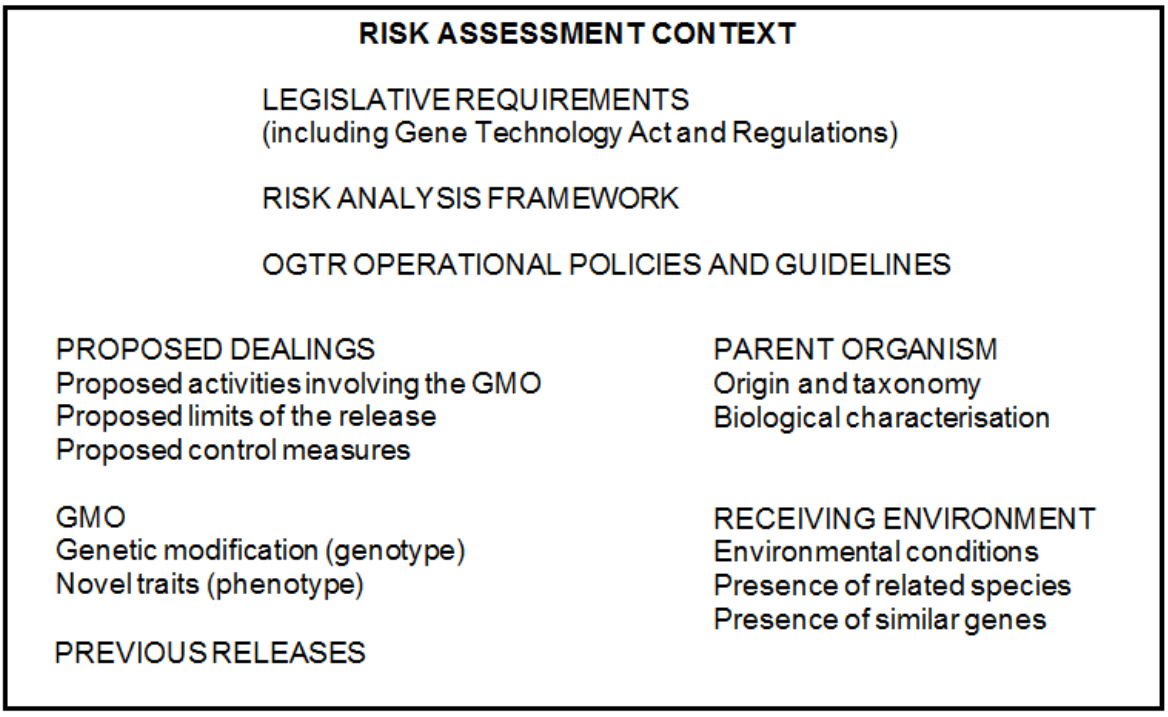

Figure 1. Summary of parameters used to establish the risk assessment context Regulatory framework

4. Sections 50, 50A and 51 of the Act outline the matters which the Gene Technology Regulator (the Regulator) must take into account, and who must be consulted, when preparing the Risk Assessment and Risk Management Plans (RARMPs) that inform the decisions on licence applications. In addition, the Regulations outline further 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, location 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.

6. 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. The advice from the prescribed experts, agencies and authorities and how it was taken into account is summarised in Appendix A. No public submissions were received.

7. The *Risk Analysis Framework* (OGTR 2013) explains the Regulator's approach to the preparation of RARMPs in accordance with the legislative requirements. 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.

1.1 Interface with other regulatory schemes

8. 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 and Water Resources. These dealings may also be subject to the operation of State legislation declaring areas to be GM, GM free, or both, for marketing purposes.

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

10. 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 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 vaccine, and risks associated with import, transport and disposal of the GMO as well as shedding of the GMO from trial participants.

11. 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, 2016). 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 and provided annotations to it (Therapeutic Goods Administration, 2018), which provides overarching guidance for conducting clinical trials in Australia which fall under TGA regulation.

12. 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, 2015). 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.

13. 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.

14. The Department of Agriculture and Water Resources administers Australian biosecurity conditions for the importation of biological products under the *Biosecurity Act 2015*. Biological products include animal or microbial derived products such as foods, therapeutics, laboratory materials and vaccines (including GM vaccines). Import of GM vaccine is subject to regulation by the Regulator and the Department of Agriculture and Water Resources.

Section 2 The proposed dealings

15. Clinical Network Services (CNS) Pty Ltd has proposed clinical trials of a GM live attenuated respiratory syncytial virus (RSV) vaccine. The purpose of the clinical trials is to assess the safety, tolerability, immunogenicity and efficacy of the GM vaccine against RSV disease. The GM vaccine will be manufactured in the USA and imported into Australia. The GM vaccine will be administered to healthy adults by intranasal spray, and samples that may contain GMOs will be collected from trial participants for analysis in laboratories within Australia or exported for testing overseas.

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

- import the GMO
- conduct experiments with the GMO
- transport the GMO
- dispose of the GMO

and possession, supply or use of GMO for the purposes of, or in the course of, any of the above.

2.1 The proposed limits of the dealings (duration, size, location and people)

17. The trials would run over a five year period from the date of issue of the licence.

18. The trials would take place at clinical sites throughout Australia. While clinical sites have not been finalised, participating sites are likely to be located in Melbourne, Sydney, Brisbane, Adelaide and/or Perth.

19. The applicant intends to enrol a maximum of 50 participants in the initial trial. Subsequent trials with up to 300 additional participants may also be performed within the period of the licence.

20. Only trained and authorised staff will be permitted to deal with the GM vaccine.

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

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

- requiring that the GM vaccine be administered by appropriately trained medical staff in clinical facilities and in accordance with ICH-GCP and WHO Universal Precautions
- requiring that clinical trial staff handling and administering the GM vaccine wear and use protective clothing and equipment
- instructing trial participants on measures intended to minimise interpersonal spread of the GM vaccine, including respiratory hygiene and cough etiquette
- instructing trial participants to seal soiled tissues in a container and return them to the

clinical site for disposal

- requiring that waste generated at clinical trial sites be disposed of following standard clinical waste disposal practices, in accordance with Commonwealth and state legislation
- requiring that the GM vaccine is transported and stored in accordance with relevant guidelines and regulations, including the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*.

2.3 Details of the proposed activities

2.3.1 Conduct of the clinical trials

22. The international trial sponsor is Codagenix, Inc. based in the USA. Codagenix has contracted CNS to run the clinical trials and manage regulatory compliance in Australia. CNS will be the local study sponsor and the Clinical Research Organisation (CRO) for the proposed trials in Australia. CNS will conduct monitoring visits at each site and periodic audits to ensure compliance with regulatory requirements.

23. The trials will involve healthy adult male and female participants. The applicant has not yet formally engaged any clinical sites at which to conduct the trials.

24. Each trial would be divided into four stages:

- Screening: Medical history and health status of prospective volunteers will be examined and their suitability to participate in the trials assessed.
- Treatment: Participants in the initial trial will receive two doses approximately four weeks apart at a single dose level. The maximum dose of the GM vaccine a participant will receive will be 10^7 plaque-forming units (pfu). The GM vaccine will be delivered intranasally using a nasal sprayer. If there is a subsequent trial, or an extension of the first trial, the dose and number of inoculations may be modified for subsequent participants based on initial results.
- Monitoring: After administration of the GM vaccine, participants will remain at the clinical trial site for monitoring for 60 to 90 minutes, after which time they can leave the clinical site. Blood and urine samples will be collected from participants after inoculation, at times that have yet to be determined.
- Follow-up: Participants will return for follow-up visits to the clinical trial site after inoculation, at times that have yet to be determined.

25. All staff handling, preparing and administering the GMO at the clinical trial site will be trained in licence conditions and relevant procedures.

2.3.2 Selection of trial participants

26. Inclusion and exclusion criteria for trial participants help ensure the safety of the individuals involved in the trials.

27. Trial participants will be limited to healthy adult males and females.

28. Exclusion criteria include:

- immune deficient or immune suppressed individuals
- those with cardiovascular or pulmonary disorders (being risk factors for more severe clinical RSV disease)
- women who are pregnant, planning to become pregnant, or breastfeeding.

29. A medical member of the study team will explain the trial requirements and the Participant Information and Informed Consent Form (PIICF) to the prospective participants. The Investigator may

exclude a person who, in their professional judgement, appears unable or unwilling to comply with the instructions (see below) or who may be at risk of an adverse outcome or serious complications from the GM vaccine.

2.3.3 Instructions to trial participants

30. The PIICF, which participants must agree to before being enrolled in the trial, will indicate to participants that they will be receiving a genetically modified vaccine, and include instructions intended to minimise interpersonal spread of the GM vaccine, including:

- to maintain hygiene measures including frequent handwashing, respiratory hygiene and cough etiquette
- not to care for immunosuppressed or immunodeficient persons and to avoid contact with such persons for at least ten days after inoculation
- not donate tissues or organs while being treated with the GM vaccine
- not to donate blood and blood products during the study and for 6 months after the end of the study
- and, for women of childbearing potential, to use effective method(s) of contraception while participating in the study, so as to avoid pregnancy.

31. The applicant indicated that participants would also likely be instructed to avoid pregnant women for one week after inoculation to avoid transmission of the GMO to pregnant women and unborn foetus.

32. These instructions will also be explained to prospective participants during initial screening.

2.3.4 Handling of the GMO

Procedures

33. Written authorisation from the principal investigator would be required before any GM vaccine is dispensed and prepared by a qualified pharmacist designated and trained for this study.

34. Preparation and dilution will be conducted in a class II biosafety cabinet (BSC) at the clinical trial site pharmacy. Concentrated GM vaccine will be diluted to the required dose and drawn into a 1.0 mL syringe. The syringe will contain a volume of about 250 microlitres of the diluted vaccine. A nasal sprayer will be attached to the syringe to produce an aerosol when delivered to the participant. No sharps will be used when preparing the GM vaccine.

35. After receipt of the diluted GM vaccine, the principal investigator, sub-principal investigator or nurse will administer the GM vaccine spray into one nostril of the participant. Only the trial participant and two clinical staff will be in the room during GM vaccine administration.

Safety considerations

36. The applicant proposed that clinical trial staff who are pregnant, immunocompromised or immunosuppressed would be excluded from handling or administering the GM vaccine.

37. When preparing, handling and administering the GM vaccine, the pharmacist will wear personal protective equipment (PPE) including disposable gloves, laboratory gown, surgical mask and eye protection. The clinical staff administering the GM vaccine will wear PPE including gloves and a surgical mask to protect their nose and mouth from aerosols.

38. When preparing, handling and administering the GM vaccine and monitoring the participant after inoculation at the clinical trial site, all staff will follow relevant institutional policies and procedures based on Universal Precautions (WHO, 2007) and 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 recognised and unrecognised sources in the clinical setting. Appropriate practices recommended by the guidelines

include (but are not limited to) hand hygiene, safe handling of potentially contaminated equipment or surfaces in the patient environment, wearing appropriate PPE, respiratory hygiene/cough etiquette, and waste management.

2.3.5 Transport, storage and analysis of the GMO and patient samples

39. The GM vaccine will be manufactured according to current Good Manufacturing Practice guidelines in the USA and imported into Australia.

40. During import and transport, the GM vaccine solution will be contained in 1 mL glass vials within a polybag secondary container. The vials in the polybag will be separated with absorbent wadding. The secondary container will be labelled to indicate that the package contains a GMO. The secondary container will be contained in a polystyrene outer container.

41. Commercial courier companies that are highly experienced with transport requirements for GMOs and infectious organisms, internationally and within Australia (e.g. World Courier), will import and transport the GMO, as well as export samples collected from trial participants.

42. Storage of the GMO before distribution to individual clinical trial sites will be at a secure storage/distribution centre, such as Cryosite.

43. Packaging and transport of the GMO will be in accordance with the International Air Transport Association (IATA) Dangerous Goods Regulations for shipping classification UN 3373 (Biological Substance, Category B) and, within Australia, the *Australian Code for the Transport of Dangerous Goods by Road & Rail* (National Transport Commission, 2017).

44. For all storage and transport within the clinical trial site and off-site within Australia, the GMO will be stored and transported according to the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*.

45. The GMO will be stored at the clinical trial site pharmacy after it is received. Once at the pharmacy, the secondary container will be removed from the polystyrene container and stored in a secure freezer with access restricted to pharmacy and clinical staff.

46. Blood and urine samples will be collected by qualified staff from trial participants at the clinical trial site. The facilities analysing/testing the samples are yet to be identified. Analysis of samples may be conducted at the clinical trial site, sent off-site to other testing laboratories in Australia, or exported for analysis overseas.

47. The forms accompanying the samples, as well as the labelling on the primary and outer container of the samples will indicate that it contains a GMO. The outer container will also be labelled with details of the applicant. Transport within Australia of patient samples will be in accordance with the *Australian Code for the Transport of Dangerous Goods by Road & Rail* (National Transport Commission, 2017). Export of samples will be packaged in accordance with IATA UN 3373, Biological Substance Category B.

48. Sample analysis in Australia may be conducted by external service providers including pathology laboratories and contract laboratories, which may be accredited by the National Association of Testing Authorities (NATA) and/or certified as PC2 facilities by the Regulator.

49. Pathology laboratories must meet specified quality standards to be accredited. The *Health Insurance (Accredited Pathology Laboratories – Approval) Principles 2002* set out the specifics of pathology accreditation and its requirements. The National Pathology Accreditation Advisory Council (NPAAC) plays a 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. Certified PC2 facilities must comply with guidelines issued by the Regulator.

50. Safe work practices in laboratories must also comply with the requirements of the *Work Health and Safety Act 2011* (Commonwealth) and state legislation related to work health and safety. Laboratories also follow the Australia/New Zealand Standard 2243.3 *Safety in laboratories Part 3: Microbiological safety and containment* (Standards Australia/New Zealand, 2010). This Standard sets out the requirements, responsibilities and general guidelines relating to safe handling and containment of microorganisms. It stipulates that human samples be handled in PC2 containment as a minimum standard.

51. NATA is Australia's national accreditation body for the accreditation of laboratories, and is also a compliance monitoring authority for the Organization for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice. NATA provides independent assurance of technical competence and integrity of organisations offering testing services.

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

52. After handling the GMO, work surfaces will be decontaminated with an appropriate chemical disinfectant such as hospital-grade disinfectants containing 5.25% sodium hypochlorite solution, following standard institutional procedures.

53. The applicant proposed that participants vaccinated with the GMO would be instructed that for ten days after vaccination they should seal soiled tissues and other materials used to collect respiratory secretions inside a primary container (a sealable plastic bag), place these in a secondary container provided by the clinical site, and store this in a place inaccessible to children and animals before returning it to the clinic for disposal as clinical waste. These practices will be explained to participants during initial screening and documented in the PIICF to which participants must agree before being enrolled in the trial. A log will be maintained at each site to record return of containers.

54. Any unused GMO will be destroyed when the trial is complete. Unused or expired GMO stocks will be placed in containers which are security sealed, tagged and loaded into secure destruction bins, and incinerated by an external waste contractor. These stock solutions will be triple contained during transport.

55. Contaminated waste, including used PPE, syringes, nasal sprayers, and soiled waste returned to the clinical site by trial participants, will be discarded into clinical waste containers. Contaminated waste will be disposed of by each clinical site following standard institutional procedures and in accordance with the requirements of the *Work Health and Safety Act 2011* (Commonwealth), relevant state legislation and the *Industry Code of Practice for the Management of Clinical and Related Wastes* ((BWI), 2010). This Industry Code of Practice details requirements for clinical waste including waste segregation, packaging, labelling, storage, transport and accountability. The applicant has stated that incineration of waste is likely, but decontamination by steam sterilisation or chemical treatment is also possible.

56. All staff working at the clinical trial site, including cleaners, will be trained in handling and disposing of infectious clinical waste and will follow standard institutional procedures such as wearing PPE when handling clinical waste, hygiene practices and disposal of clinical waste.

57. Contractors who transport and decontaminate clinical waste will observe safety precautions appropriate for handling infectious waste. These contractors will have been selected based on their experience and capability in disposing of clinical waste.

2.3.7 Contingency plans

58. The outer container of the GMO and samples will be labelled with instructions to contact the applicant in the event of a spill, and warning text describing appropriate spill clean-up procedures, required PPE and disposal methods. In the event of accidental spill of the GMO, these spill clean-up procedures will be implemented.

59. In the event of accidental human exposure to the GMO, the applicant has proposed the following: wash hands or use alcohol hand sanitiser, flush eyes with water if eyes were exposed to the GMO, and report any suspected adverse events that are typical of RSV infection.

60. Should any adverse event occur to a trial participant, or a person working at the clinical trial site is exposed to the GMO during the clinical trial, they would be assessed by the Investigator or medical staff at the relevant clinical site and appropriate medical intervention determined and administered, if necessary.

2.3.8 Record keeping

61. At each clinical site, the investigator/pharmacist, or delegated person, will maintain an accountability log for the GMO detailing the dates and quantities dispensed. The GMO accountability records will be verified by CNS during clinical site visits. All documentation related to the GMO will be accounted for at each step including import, transport, receipt, authorisation for use, dispensing and destruction. These records will be made available to the Regulator on request. Records of training of the clinical trial staff will be kept at each clinical trial site and also be made available to the Regulator on request.

Section 3 The parent organism

62. The parent organism is *human respiratory syncytial virus* (RSV) which belongs to the genus *Orthopneumovirus* and family *Pneumoviridae* (Rima et al., 2017).

63. RSV is the leading viral agent of serious paediatric respiratory tract disease worldwide. RSV also is a significant cause of morbidity and mortality in the elderly, with an impact approaching that of non-pandemic influenza virus. RSV also makes a substantial contribution to upper respiratory tract disease in individuals of all ages (Collins and Graham, 2008; Collins and Melero, 2011).

3.1 Basic Biology

64. RSV is an enveloped, non-segmented, negative-sense, single-stranded RNA virus. Its genome is approximately 15,222 nucleotides in length, and has 11 genes encoding 11 proteins. The RSV particles consist of a nucleocapsid surrounded by a lipid envelope (Tripp, 2009; Rima et al., 2017).

65. The RSV genome contains two non-structural genes (NS1 and NS2), followed by the nucleocapsid (N), phosphoprotein (P), matrix (M), small hydrophobic (SH), surface attachment glycoprotein (G), surface fusion glycoprotein (F), second matrix (M2) and RNA-dependent RNA polymerase (L) genes (Figure 2 and Table 1). The RNA is negative-sense (3’ to 5’) as it is complementary to mRNA (Tripp, 2009; Rima et al., 2017).

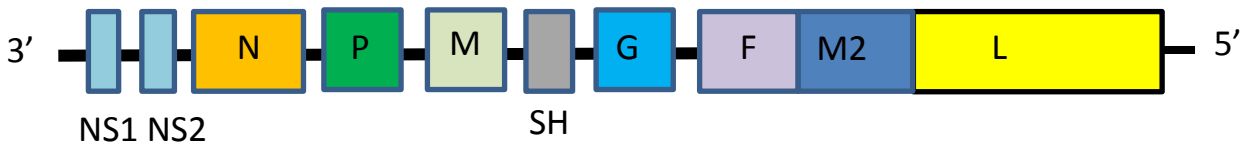

Figure 2. Genome organisation of RSV. Each box represents a gene from which a separate mRNA is produced, encoding the viral proteins: non-structural (NS); nucleocapsid (N); phosphoprotein (P); matrix (M); small hydrophobic (SH); surface attachment glycoprotein (G); surface fusion glycoprotein (F); second matrix (M2); and RNA-dependent RNA polymerase (L).

Table 1. Summary of RSV gene function (Tripp, 2009; Rima et al., 2017).

Gene	Brief description of function
NS1 and NS2	Inhibit the synthesis and action of the host interferon responses, and inhibit apoptosis.
N	Viral RNA binding protein that has a central role in transcription and replication of the viral genomic RNA.
P	A key component of the viral RNA-dependent RNA polymerase complex, which has two general functions as a transcription and replication factor.
M	Functionally inactivate nucleocapsid transcription prior to packaging, and to mediate nucleocapsid association with the nascent envelope.
SH	May be involved in cell-to-cell fusion and may play a role as an ion channel.
G, F	Envelope glycoproteins involved in attachment and fusion of the virion to host cell.
M2-1	Enhances virus RNA synthesis through its action as a processivity factor.
M2-2	Involved in the switch of viral RNA synthesis from transcription to replication.
L	Large RNA-dependent RNA polymerase that initiates viral transcription in the cytoplasm.

66. Virions attach to target cells through the G glycoprotein. Attachment is mediated by interaction of heparin-binding domains on the G glycoprotein with cell surface glycosaminoglycans. RSV penetrates the cell by fusion of the viral envelope with the plasma membrane, a process associated with F glycoprotein, and release of the nucleocapsid into the cytoplasm. Transcription of mRNA occurs from a single promoter near the 3' end of the genomic RNA, resulting in a series of subgenomic mRNAs. Replication takes place in the cytoplasm and the viral genome does not integrate into the host genome (Tripp, 2009).

3.2 Host range

67. RSV was first isolated in 1956 from a colony of captive chimpanzees with upper respiratory tract disease resembling the common cold. It was independently isolated from human infants with lower respiratory tract disease a few years later. The virus was eventually determined to be of human origin (Collins and Graham, 2008; Tripp, 2009).

68. RSV infects mainly humans in the natural environment. Wild gorillas and chimpanzees in Africa experienced RSV infection and respiratory disease (Kondgen et al., 2008; Grutzmacher et al., 2016).

69. Various animal species are semi-permissive to infection and viral replication, and can be experimentally infected with RSV. These include cotton rats, mice, ferrets, guinea pigs, hamsters, chinchillas, lambs and some nonhuman primates. Inoculation of these animals with large doses of RSV results in little or no clinical signs of disease. The only animal that approaches human permissiveness to infection and disease is the chimpanzee. There is no known animal reservoir for RSV (Tripp, 2009; Canada, 2011; Taylor, 2017).

3.3 Clinical disease

70. RSV is a common respiratory virus that usually causes mild, cold-like symptoms in adults and older healthy children. Reinfection with RSV is common throughout life, and the symptoms are

generally less severe, of shorter duration and limited to the upper respiratory tract or asymptomatic (Hall et al., 1991; Collins and Graham, 2008; Collins and Melero, 2011).

71. Infants, young children, the elderly and people with an immunodeficiency or immunosuppression disorder are at an increased risk of severe RSV infection. Other factors that compromise the ability to control and withstand a respiratory tract infection include premature birth, low birth weight, congenital heart disease, cardiopulmonary disease and low titres of RSV-specific serum antibodies. Death may result following severe RSV infection in high-risk individuals. Other factors that may predispose to RSV infection include low socioeconomic status, tobacco use, exposure to smoke and family history of atopy or asthma (Collins and Graham, 2008; Collins and Melero, 2011; Paes et al., 2011).

72. RSV has an incubation period of 2 to 8 days after exposure. RSV infections usually begin with upper respiratory tract disease, which may progress to lower respiratory tract disease. Primary infection can also manifest as lower respiratory tract disease, pneumonia, bronchiolitis, or tracheobronchitis. Common clinical symptoms of RSV infection include rhinorrhea, sneezing, cough, pharyngitis, sore throat, headache, fatigue and fever. In some cases, otitis media may occur (Collins and Graham, 2008; Canada, 2011; Collins and Melero, 2011). Some clinical symptoms including rhinorrhea can last up to 41 days post-infection in healthy RSV-infected adults (Hall et al., 1978).

3.4 Pathogenesis

73. Infection is normally restricted to the superficial cells of the respiratory epithelium. RSV primarily infects human epithelial cells within the nasopharynx. The airways become obstructed due to sloughing of epithelial cells, mucus secretion and accumulation of immune cells (Collins and Graham, 2008).

3.5 Shedding

74. RSV is released from infected epithelial cells of the throat and nasopharynx, and into respiratory secretions. At the beginning of illness, RSV replicates in the nasopharynx of an infected host, reaching titres between 10^4 and 10^7 tissue culture infectious dose 50% ($TCID_{50}$)/mL in nasal secretion in infants. The titre decreases over time during recovery (Tripp, 2009).

75. RSV RNA has also been detected in saliva, stool and sweat samples from hospitalised infants. No RSV RNA was detected in their urine or blood. However, further studies are required to determine if the RSV RNA detected in these samples represents infectious virions (von Linstow et al., 2006).

76. Healthy adults inoculated with RSV shed the virus for an average duration of 9-10 days post-inoculation, with peak viral shedding on day 5 post-inoculation. No viral shedding was detected on day 28 post-inoculation (Falsey et al., 2003; Lee et al., 2004).

77. Prolonged RSV shedding has been observed in immunocompromised adults with cancer, with a median duration of 80 days and a range of 35-334 days (Lehners et al., 2016).

3.6 Transmission

78. RSV is transmitted by aerosols, direct contact with infectious secretions or via fomites; however, close contact with infected individuals, or exposure of nasal or conjunctival mucosa with contaminated hands, is required for transmission (Canada, 2011).

79. Transplacental transmission has been demonstrated in rats, although no abnormal histology was observed in the foetal and newborn lungs and airways (Piedimonte et al., 2013). RSV has been detected in human cord blood (Fonceca et al., 2017), and RSV may have been transmitted to an unborn child by a mother infected with RSV during pregnancy (Manti et al., 2017). The newborn experienced viral pneumonia and required neonatal intensive care.

80. RSV infection and respiratory disease reported in wild gorillas and chimpanzees in Africa may have been transmitted from humans (Kondgen et al., 2008; Grutzmacher et al., 2016).

81. There is limited information on non-primate animal transmission of RSV in the natural environment. In an experiment, transmission of the virus to RSV-naïve ferrets cohoused with RSV-inoculated ferrets was detected. Transmission of the virus occurred when the RSV-inoculated ferrets shed high amounts of the virus (Chan et al., 2017).

3.7 Tissue distribution

82. It appears that RSV can spread and infect tissues and cells outside the respiratory tract, even though the presence of viraemia during RSV infection is rarely documented in the literature. A study detected the presence of viraemia during the course of RSV infection in neonates. It was concluded that viraemia may be a frequent occurrence in neonates and young children (Rohwedder et al., 1998). It has been shown that human bone marrow stromal cells in adults and children can be infected with RSV *in vivo* (Rezaee et al., 2011). Other sites where RSV has been detected include myocardium, cerebrospinal fluid and liver samples from human patients including infants, people with immunodeficiency disorder and other concomitant medical conditions (Eisenhut, 2006).

3.8 Persistence after infection

83. RSV may persist for long periods in immunologically privileged sites in the lung, avoiding immune detection and elimination. In mice, viral RNA was detectable up to 77 days after inoculation and its long-term presence was associated with disease severity (Chavez-Bueno et al., 2005; Estripeaut et al., 2008). In humans, RSV RNA was detected in the sputum over a two-year period, suggesting viral persistence in the lower airways (Wilkinson et al., 2006).

84. RSV genomic RNA has been detected in human bone marrow stromal cells from both adult and paediatric donors, raising the possibility of an extrapulmonary site of infection and persistence (Rezaee et al., 2011).

3.9 Prevention and treatment of infection

85. There are currently no registered vaccines against RSV. Treatment of acute RSV lower respiratory disease mainly involves supportive care, including administration of intravenous fluids, humidified oxygen and mechanical ventilation. Prophylaxis with RSV neutralising antibodies has been effective in reducing RSV disease in young infants; Palivizumab prophylactic treatment is recommended for infants and children at high risk of RSV disease (Canada, 2011; Collins and Melero, 2011; Centers for Disease Control and Prevention, 2017b).

3.10 Recombination

86. In an *in vitro* experiment, both non-homologous and homologous recombination events have been detected between two different mutant RSV strains co-infecting a cell. Because the recombinant virus was detected in only one of the six cell culture co-infections established in this study, this finding suggests that the formation of viable recombined RSV is rare in cell culture and therefore likely to be even more uncommon in nature (Spann et al., 2003). There are no reports of recombination between RSV strains occurring in the natural environment.

3.11 Environmental survival

87. RSV can survive on a variety of inanimate objects, such as table tops, rubber gloves, cloth gowns and tissues ranging from 30 min to 6 hours (Pirtle and Beran, 1991). RSV is generally very vulnerable to environmental changes, particularly temperature and humidity. It loses up to 90% infectivity at room temperature after 48 hours, and up to 99% infectivity at 1°C after 7 days (Canada, 2011).

3.12 Susceptibility to chemical treatment

88. RSV is susceptible to ether, chloroform and a variety of detergents, including 0.1% sodium deoxycholate, sodium dodecyl sulphate and Triton X-100. It is also sensitive to hypochlorite, formaldehyde, glutaraldehyde, quaternary ammonium compounds and iodophores (Centers for Disease Control and Prevention, 2008; Canada, 2011). A 1:10 dilution of bleach totally inactivated RSV in 5 minutes (Krilov and Harkness, 1993).

Section 4 The GMO, nature and effect of the genetic modifications

4.1 The genetic modifications

89. The GMO is a live attenuated virus based on the RSV A2 strain. This strain was modified firstly by a deletion of the 112 nucleotide fragment of the downstream non-coding region of the SH gene, and by synonymous codon changes (i.e. changes to the nucleotide sequence that do not change the encoded amino acid) for the last three codons of the SH open reading frame (ORF). These nucleotide changes were made to improve stability during growth in *Escherichia coli* and do not affect the efficiency of virus replication *in vitro* or in mice. This modified RSV genome is referred to as "wild-type rRSV" in Le Nouen et al's studies (2014; 2017).

90. The RSV nucleotide sequence has been further modified by a process termed codon pair deoptimisation (CPD). CPD involves determining all possible synonymous codon changes, and selecting codon pairs that are used in humans at a low frequency. Codon pair deoptimised viral genes are translated with lower efficiency in the host cell and are attenuated compared with the wild-type virus (Le Nouen et al., 2014). Influenza viruses, polioviruses and porcine reproductive and respiratory syndrome viruses modified by CPD have been shown to replicate to lower titres in cell culture and in animals (Coleman et al., 2008; Ni et al., 2014; Baker et al., 2015). The GM RSV genome was chemically synthesised by *de novo* DNA synthesis to incorporate a codon pair deoptimised L open reading frame (ORF) sequence containing 1,378 synonymous nucleotide mutations. The resulting GM virus is referred to as MinL RSV. The amino acid sequence of the L protein encoded by MinL RSV is identical to that of the wild-type RSV (Le Nouen et al., 2014).

91. In a temperature stress experiment, the MinL RSV was passaged multiple times *in vitro* under increasing temperatures up to 40°C to test the virus' stability. During this process certain additional amino acid mutations arose in high frequency, specifically N [K136R], P [E114V], M2-1 [N88K] and L [T1166I]. Therefore, these four mutations were introduced into the N, P, M2 and L genes of the MinL RSV genome. Compared with MinL RSV, the combined effect of these additional single amino acid mutations conferred an ability to grow at a higher temperature of 40°C *in vitro.*

92. The resultant GMO is the GM RSV vaccine strain proposed for clinical trial. This GM strain, referred to as MinL4.0 RSV was considered an improvement on MinL RSV as a potential vaccine strain for a number of reasons: a) MinL4.0 RSV exhibited increased replication compared with MinL RSV *in vitro*, which is important for vaccine manufacture; b) MinL4.0 RSV did not accumulate additional mutations after it was passaged in temperature stress experiments; and c) MinL4.0 RSV replicated poorly *in vivo* compared to MinL RSV but was as immunogenic as wild-type rRSV (Le Nouen et al., 2017).

4.2 Characterisation of the GMO

4.2.1 The effects of CPD in vitro

93. The effect of CPD on several viral properties of MinL RSV was studied *in vitro*. The growth of MinL RSV in Vero cells was delayed and reduced, and the amount of viral mRNA (indicative of viral gene transcription) and viral protein production by MinL RSV were greatly reduced compared with the wild-type rRSV (Le Nouen et al., 2014).

4.2.2 The effects of CPD in vivo

94. In non-human primates, MinL RSV was detected in nasopharyngeal swabs and tracheal lavage samples for up to 5 days post-inoculation, whereas for the wild-type rRSV the duration was up to 10 days post-inoculation. The titres of MinL RSV shed in these samples were 1000-fold lower than wild-type rRSV. Despite the attenuated properties of MinL RSV, titres of serum antibodies induced by MinL RSV were not statistically different from those of the wild-type rRSV (Le Nouen et al., 2014).

4.2.3 The effects of amino acid changes in vitro

95. The effect of the additional amino acid changes in the N, P, M2 and L genes on several viral properties of MinL RSV was studied *in vitro*. The amount of viral mRNA and protein expression by MinL4.0 RSV were increased modestly compared with the MinL RSV, but remained greatly reduced compared with the wild-type rRSV (Le Nouen et al., 2017).

4.2.4 Viral replication of the GMO in vivo

96. Attenuation of the MinL4.0 RSV was investigated *in vivo* in mice and hamsters. MinL4.0 RSV exhibited greatly reduced viral replication in the nasal turbinates and lungs compared with the wild-type rRSV and MinL RSV, and a lower proportion of animals became infected with MinL4.0 RSV (Le Nouen et al., 2017).

4.2.5 Immunogenicity of the GMO

97. MinL4.0 RSV induced titres of serum antibodies against RSV not statistically different from the wild-type rRSV in inoculated hamsters. MinL4.0 RSV-inoculated hamsters challenged with the wild-type rRSV showed no detectable wild-type rRSV replication. The data suggest that the MinL4.0 RSV provides protective immunity, despite its attenuated nature (Le Nouen et al., 2017).

4.2.6 Genetic stability of the GMO

98. The genetic stability of MinL4.0 RSV was assessed in a temperature stress test involving four passages at 39°C followed by four passages at 40°C, corresponding to two months of continuous passage. Sequencing of the complete genome of the final passage of 10 different stressed lineages did not detect any additional mutations, other than the introduced mutations (Le Nouen et al., 2017).

Section 5 The receiving environment

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

5.1 Site of release

100. The intended primary receiving environment would be the nose, nasal turbinates and nasopharynx of trial participants, to be delivered via a nasal sprayer as an aerosol.

101. The secondary receiving environment would be the room and the clinical trial site where the GMO is dispensed, administered and waste disposed of. All clinical sites involved in the study would be equipped to handle infectious agents and procedures would be conducted in accordance with institutional policies based on Universal Standard Precautions (WHO, 2007) and the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* (National Health and Medical Research Council, 2010).

102. The principal route by which the GMO may enter the wider environment is by shedding from inoculated trial participants once they leave the clinical trial site and return home. The tertiary receiving environment includes the trial participants' homes and any places they visit during the period when the GMO is replicating and shedding.

5.2 Related viral species in the receiving environment

103. The presence of related viral species provides a baseline for assessment of the potential impacts of the GMO, and may offer an opportunity for the horizontal transfer of modified genetic material from the GMO to other organisms in the receiving environment.

104. As indicated in Section 3, wild-type RSV is a common human pathogen in Australia. In Australian adults with "influenza-like" symptoms, the rate of detection of RSV is 3.1% (Varghese et al., 2018). Using the BLAST online tool (National Center for Biotechnology Information (NCBI), 2017), comparison of the full genomic sequences of the MinL RSV (Genbank accession number: KJ817800), containing the CPD L ORF, and other RSV strains, which may be circulating in the environment, reveals that they range between 85% and 91% identical.

105. Three known members of the genus *Orthopneumovirus* are present in Australia. These viruses are highly species-specific, and are not known to infect humans: *bovine orthopneumovirus* infects cattle (Easton et al., 2004); *murine orthopneumovirus* infects mice and hedgehogs (Madarame et al., 2014; Rima et al., 2017); and *swine orthopneumovirus* infects pigs (Hause et al., 2016). Their host specificities means they are unlikely to occur in the same host in the natural environment.

106. One other member of the family *Pneumoviridae* is known to cause respiratory disease in humans, *human metapneumovirus* in the genus *Metapneumovirus* (Rima et al., 2017). Similar to RSV, *human metapneumovirus* causes upper and lower respiratory disease in people of all ages, especially among young children, the elderly and people with weakened immune systems (Centers for Disease Control and Prevention, 2017a). Unlike RSV, *human metapneumovirus* lacks NS1 and NS2 genes, and has a different gene order (*3'-N-P-M-F-M2-SH-G-L-5'*) (van den Hoogen et al., 2002; Tripp, 2009).

107. Another recently identified virus which may belong to the family *Pneumoviridae* infects bats (Drexler et al., 2012). However, RSV is not known to infect bats.

5.3 Other relevant environmental factors

108. Environmental factors relevant to the potential persistence or spread of the GMO, or the harm it may cause, include the presence of susceptible hosts and any physical conditions that may aid or restrict transmission to these hosts.

109. Humans are the natural host for RSV. While infection of other animal species has been achieved experimentally (as discussed in Section 3.2), there are no reports of non-primate animals being infected with RSV naturally. Wild chimpanzees and gorillas have been infected with RSV in the African natural environment (Kondgen et al., 2008; Grutzmacher et al., 2016). There are no animal reservoirs for RSV.

110. RSV infection rate displays a seasonal pattern. In temperate regions of Australia, RSV infections increase in winter and spring (Roche et al., 2003).

111. Certain people who are at most risk of severe RSV infection and disease include infants, the elderly, those with immune deficiency/suppression or cardiopulmonary disease (as discussed in Section 3.3). Such groups of people may come into contact with the inoculated trial participants outside the clinical trial sites in the community or in the domestic setting.

112. There are currently no available vaccines against RSV.

Section 6 Relevant Australian and international approvals

6.1 Australian approvals

113. The GM vaccine has not previously been released in Australia. Clinical trials of the GM vaccine would also need to meet the regulatory requirements of the TGA. The GM vaccine has not yet been

imported into Australia. Import of the GM vaccine would also require a permit from the Department of Agriculture and Water Resources.

6.2 International approvals

114. A clinical trial using the MinL RSV vaccine strain to protect against RSV is currently being conducted in the USA under an Investigational New Drug authorisation (Clinicaltrials.gov identifier: NCT01459198).

Chapter 2 Risk assessment

Section 1 Introduction

115. 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.

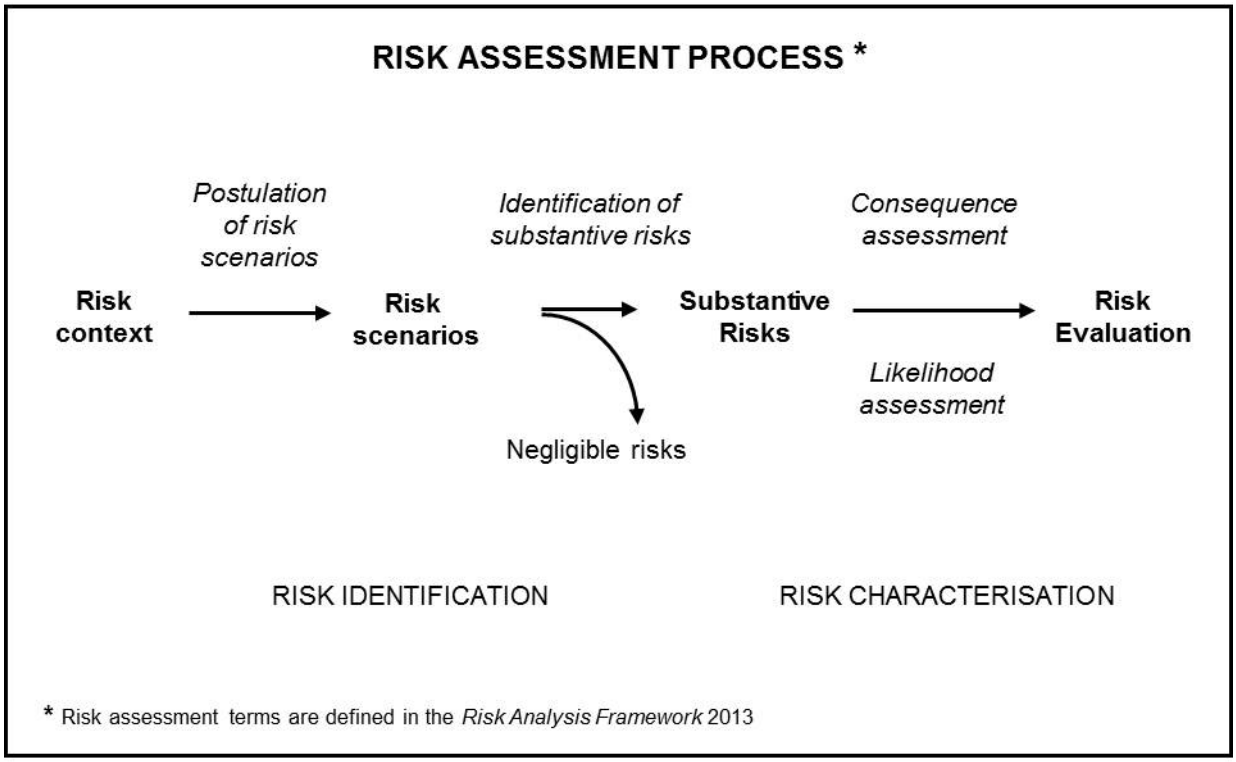

Figure 3. The risk assessment process

116. 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 in the short or long term. These are called risk scenarios.

117. 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). Risk scenarios postulated in previous RARMPs prepared for licence applications of the same or similar GMOs are also considered.

118. Postulated risk scenarios are screened to identify those that are 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.

119. 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). Risk evaluation then combines the Consequence and Likelihood assessments to estimate the level of risk and determine whether risk treatment measures are required. The potential for interactions between risks is also considered.

Section 2 Risk identification

120. Postulated risk scenarios are comprised of three components:

i. The source of potential harm (risk source).

ii. A plausible causal linkage to potential harm (causal pathway).

iii. Potential harm to people or the environment.

121. When postulating relevant risk scenarios, the risk context is taken into account, including the following factors:

- the proposed dealings, which are import, conduct of experiments, transport and disposal of the GMO, and the possession, supply and use of the GMO in the course of any of these dealings
- the proposed limits including the extent and scale of the proposed dealings
- the proposed controls to limit the spread and persistence of the GMO
- the characteristics of the parent organism and known transmission pathways and
- the environment at the sites of release.

122. As discussed in Chapter 1, Section 1.1, 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, 2015). Therefore, risk scenarios in the current assessment focus on risks posed to people other than those participating in the clinical trial, and to the environment.

2.1 Postulated risk scenarios

123. Eight risk scenarios were postulated and screened to identify substantive risks. These scenarios are summarised in Table 2, and examined in detail in Sections 2.1.1–2.1.8. Postulation of risk scenarios considers impacts of the GMO on clinical trial staff and external service providers undertaking the dealings, as well as on other people and animals with whom trial participants may come into contact.

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

Table 2. Summary of risk scenarios arising from the proposed dealings

Risk scenario	Risk source	Causal pathway	Potential harm(s)	Substantive risk?	Reasons
1	GM RSV	Exposure of clinical trial staff dispensing or administering the GMO via: i. needlestick/sharps injury; ii. inhalation of, or mucous membrane contact with, aerosols released directly from the nasal spray device, produced by trial subjects experiencing a sneeze reflex, or released during a spill of the GMO; or iii. mucous membrane contact with contaminated hands	RSV disease	No	• The applicant has stated that sharps will not be used when preparing the GMO for administration. • The GMO will be dispensed in a Class II BSC, which minimises potential exposure. • Staff dispensing or administering the GMO will be trained in good clinical practice, and follow standard precautions. • The GMO is expected to be attenuated relative to wild-type RSV, which is present in the environment. • Immunocompromised and immunodeficient staff, who may

Risk scenario	Risk source	Causal pathway	Potential harm(s)	Substantive risk?	Reasons
		⬇ Transduction of cells ⬇ Establishment of viral infection			experience more severe disease symptoms, will be advised not to handle or administer the GMO.
2	GM RSV	Unused GMO, or waste containing the GMO, disposed of from clinical trial site ⬇ Exposure of persons handling waste to the GMO ⬇ Transduction of cells ⬇ Establishment of viral infection	RSV disease	No	• Staff working in clinical trial sites will be trained in handling infectious clinical waste and follow standard institutional procedures. • Unused GMOs and contaminated waste will be placed in clinical waste containers and disposed of as infectious clinical waste, following standard clinical waste disposal practices in accordance with State legislation. • The GMO is expected to be attenuated relative to wild-type RSV.
3	GM RSV	Unintentional release of the GMO during storage or transport ⬇ Exposure of people or animals to the GMO ⬇ Transduction of cells ⬇ Establishment of viral infection	RSV disease in humans or animals	No	• The GMO will be stored securely at storage/distribution centres and clinical facilities. • Transport and storage (including within clinical sites) of the GMO will follow the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*. • The GMO is expected to be attenuated relative to wild-type RSV. • RSV is not known to cause disease in non-primates in the natural environment, and the genetic modifications are not expected to alter the host range of the GMO.
4	GM RSV	Inoculation of trial participant with the GMO ⬇ Samples containing GMO collected, transported and analysed ⬇ Exposure of collection staff, couriers or laboratory staff ⬇ Transduction of cells ⬇ Establishment of viral infection	RSV disease	No	• Samples will be collected by qualified staff at clinical trial sites. • Samples will be analysed in laboratories which adhere to appropriate safety precautions. • Samples will be double-contained during transport. • The GMO is expected to be attenuated relative to wild-type RSV.
5	GM RSV	Inoculation of trial participant with the GMO ⬇ Trial participant sheds the GMO e.g. via respiratory secretions, sweat, saliva	Increased disease burden in humans or animals	No	• Trial participants will be instructed in well-established hygiene practices intended to minimise inadvertent transmission of RSV. • Trial participants will be instructed to collect used tissues in appropriate

Risk scenario	Risk source	Causal pathway	Potential harm(s)	Substantive risk?	Reasons
		⬇ Exposure of other people (e.g. household contacts or patients in clinical trial sites, including at-risk people and pregnant women) or animals via: i. direct contact with trial participant; ii. exposure to aerosolised secretions (e.g. from sneezing); or iii. contact with contaminated items (e.g. items the trial participant has touched, or contaminated tissues/waste); ⬇ Transduction of cells ⬇ Establishment of viral infection			containers for at least 10 days after inoculation with the GMO, for return to clinical sites for disposal. • Trial participants will be instructed to avoid contacting at-risk groups. • Due to expected attenuation of the GMO, viral titres shed by trial participants are likely to be far lower than originally administered to them. • RSV is not known to cause disease in non-primates in the natural environment, and the genetic modifications are not expected to alter the host range of the GMO.
6	GM RSV	Inoculation of trial participant with the GMO ⬇ Donation of blood, blood products, organs or tissues containing the GMO ⬇ Transduction of cells in recipient ⬇ Establishment of viral infection	RSV disease	No	• Trial participants will be instructed not to donate blood, blood products, tissues or organs for a specified period. • Similar to wild-type RSV, the GMO may persist in cells or tissues within and/or outside the respiratory tract and lungs for a prolonged period. However, it is expected that disease caused by the GMO would be no worse than that due to wild-type RSV acquired by the same route.
7	GM RSV	Inoculation of trial participant with the GMO ⬇ Trial participant is already, or later becomes, infected with wild-type RSV or other *Pneumoviridae* species ⬇ Co-infection of host cells ⬇ Recombination between GM and wild-type viral genomes takes place ⬇ Novel recombinant virus infects other hosts	Increased disease burden due to novel virus with altered virulence	No	• Recombination between RSV strains or other species of the *Pneumoviridae* family has not been documented in the natural environment. • Experimental recombination between RSV strains is infrequent. • Recombination between the GMO and wild-type RSV is not expected to produce a virus more virulent than recombination involving circulating wild-type viruses.
8	GM RSV	Inoculation of trial participant with the GMO ⬇	Toxicity, allergen-icity, or	No	• Studies with the GMO have not shown unintended effects. • No toxicity, allergenicity or abnormal

Risk scenario	Risk source	Causal pathway	Potential harm(s)	Substantive risk?	Reasons
		Exposure of other people by pathways described in scenarios 1-6 ⬇ Altered characteristics of the GMO in the host ⬇ Unintended host reaction	abnormal immune response		immune responses are reported using similar RSV vaccines in clinical trials.

2.1.1 Risk scenario 1

Risk source	GM RSV
Causal pathway	Exposure of clinical trial staff dispensing or administering the GMO via: i. needlestick/sharps injury; ii. inhalation of, or mucous membrane contact with, aerosols released directly from the nasal spray device, produced by trial subjects experiencing a sneeze reflex, or released during a spill of the GMO; or iii. mucous membrane contact with contaminated hands ⬇ Transduction of cells ⬇ Establishment of viral infection
Potential harm	RSV disease

Risk source

125. The source of potential harm for this postulated risk scenario is GM RSV.

Causal pathway

126. Clinical trial staff dispensing (i.e. diluting concentrated viral stock, loading syringes and attaching the nasal sprayer) or administering the GMO could be exposed via: a needlestick/sharps injury; inhalation of droplets or aerosols released directly from the nasal spray device during administration, produced by trial subjects experiencing a sneeze reflex, or released during a spill of the GMO; or exposure of the mucous membrane of the eye to aerosols, a splash, or through contaminated hands. Staff dispensing will handle the GMO in its most concentrated form and could receive a relatively high viral dose if exposed.

127. While no reports of parenteral transmission of RSV were located, percutaneous transmission of other airborne viruses has been documented in the occupational context, and most infectious agents are capable of causing at least a local infection if inoculated directly into the skin (Dieckhaus, 2007). However, the applicant has stated that sharps will not be used when preparing the GMO for administration, thus parenteral exposure via sharps injury is not expected to occur.

128. Wild-type RSV is known to be transmitted via inhalation of aerosols containing the virus. Staff dispensing the GMO will work in a Class II BSC which will minimise exposure to aerosols.

129. RSV is also transmitted through direct contact with mucous membranes of the respiratory tract and eyes. As noted above, containment of the GMO in a Class II BSC while dispensing the GMO will prevent exposure to aerosols and provide splash protection to the face. Staff dispensing the GMO will also wear PPE including gloves and a long-sleeved laboratory gown, providing protection to the hands and arms.

130. Clinical trial staff administering the GMO will be trained in good clinical practice. Staff dispensing or administering the GMO will follow precautions including the WHO Universal Precautions and those described in 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. These precautions include wearing PPE (e.g. gloves, surgical mask and eye protection), and washing or disinfecting hands after handling potentially infectious agents. Staff administering the GMO will wear eye protection, and a surgical mask covering the nose, which will protect them from aerosols generated while administering the GMO. The use of gloves and hand washing will minimise the potential for hands to become contaminated with the GMO and subsequently contact the face.

131. If a participant sneezes during or immediately after the GMO is sprayed into the nostril, it is expected that they will follow respiratory etiquette by covering their nose and mouth, as instructed by clinical trial staff.

132. Should the GMO be spilled, a spills procedure will be implemented. After disinfecting and cleaning up the spill, staff will dispose of contaminated disposable materials and PPE, and disinfect or wash their hands. This will minimise exposure of clinical trial staff to the GMO.

Potential harm

133. Studies in animals have shown reduced replication of the CPD MinL RSV *in vivo* relative to wild-type rRSV (Le Nouen et al., 2014). Although the proposed trial represents the first in-human study, the CPD strategy was designed to reduce translation efficiency in human hosts (Le Nouen et al., 2014), and as discussed in Chapter 1, Section 4.1, has been shown to be effective in a number of other viral species(Coleman et al., 2008; Ni et al., 2014; Baker et al., 2015).

134. As discussed in Chapter 1, Section 4, four amino acid mutations were introduced into the N, P, M2 and L genes in addition to the CPD L ORF. The overall effect of these amino acid mutations was greatly reduced viral replication *in vivo* compared with the MinL RSV, thus conferring greater attenuation of the GMO. Therefore it is expected that the GMO will be highly attenuated in humans. Even if exposure occurs, otherwise healthy people infected with the GMO are expected to experience less severe disease symptoms, if any, compared with those caused by the wild-type virus.

135. Staff will be advised that individuals who are immunocompromised or immunosuppressed must not handle or administer the GMO. This will minimise opportunities for exposure of these at-risk groups.

136. The applicant has not proposed to exclude other categories of at-risk person, such as those with cardiopulmonary disease, from handling the GMO. Such individuals, already at risk of developing severe disease in response to RSV infection, may experience more severe symptoms than healthy people if infected with the GMO. It is expected, however, that any such disease symptoms would be no worse than those due to wild-type RSV, which is widespread in the Australian environment.

Conclusion

137. Risk scenario 1 is not identified as a substantive risk because exposure is minimised by the proposed practices, and the GMO is expected to cause less severe disease in healthy or at-risk people than the wild-type virus. Therefore, this risk could not be greater than negligible and does not warrant further detailed assessment.

2.1.2 Risk scenario 2

Risk source	GM RSV
Causal pathway	Unused GMO, or waste containing the GMO, disposed of from clinical trial site ⬇ Exposure of persons handling waste to the GMO ⬇ Transduction of cells ⬇ Establishment of viral infection
Potential harm	RSV disease

Risk source

138. The source of potential harm for this postulated risk scenario is GM RSV.

Causal pathway

139. Waste containing the GMO, and any unused GMO stocks, will be disposed of from clinical trial sites. Clinical staff and other persons handling these materials, such as clinical trial site cleaners and external waste contractors, may be exposed to the GMO.

140. Contaminated waste, including used PPE, syringes, nasal sprayers, and soiled waste returned to the clinical site by trial participants, will be promptly discarded into clinical waste containers, which would minimise exposure to contaminated material once it has been discarded.

141. Contaminated waste will be disposed of by each clinical site following standard institutional procedures and in accordance with the requirements of the *Work Health and Safety Act 2011* (Commonwealth), relevant state legislation and the *Industry Code of Practice for the Management of Clinical and Related Wastes* ((BWI), 2010). This Industry Code of Practice details requirements for clinical waste including waste segregation, packaging, labelling, storage, transport and accountability. The applicant has stated that incineration of waste is likely, but decontamination by steam sterilisation or chemical treatment is also possible. All three methods are considered appropriate for disposal of clinical waste containing the GMO.

142. All staff working at the clinical trial site, including cleaners, will be trained in handling and disposing of infectious clinical waste and will follow standard institutional procedures such as wearing PPE when handling clinical waste, hygiene practices and disposal of clinical waste.

143. Contractors who transport and decontaminate clinical waste will observe safety precautions appropriate for handling infectious waste. These contractors will have been selected based on their experience and capability in disposing of clinical waste. These measures will minimise the potential for exposure to the GMO.

144. Unused or expired GMO stocks will be placed in containers which are sealed, tagged and loaded into secure destruction bins, and incinerated by an external waste contractor. These stock solutions represent the most concentrated source of GMO waste, but given they will be triple contained during transport, it is highly unlikely that waste handlers would be exposed to the GMO.

145. Environmental stability of RSV is low. The GMO stock solutions must be stored frozen, and can remain at room temperature for 4 hours prior to use. Discarded GMO stocks will be stored and transported at ambient temperature, at which they are expected to deteriorate over several days (Canada, 2011), diminishing their infectivity in the event that exposure occurs.

Potential harm

146. As described in Risk Scenario 1, the GMO is expected to be attenuated in humans and would result in disease no worse than that caused by the wild-type virus. As discussed above, this applies equally to healthy staff and any at-risk individuals who may handle the GMO.

Conclusion

147. Risk scenario 2 is not identified as a substantive risk because the potential for exposure is minimised by discarding contaminated waste into clinical waste containers followed by disposal via the clinical waste stream following standard clinical waste practices. The GMO is expected to cause less severe disease than the wild-type virus. Therefore, this risk could not be greater than negligible and does not warrant further detailed assessment.

2.1.3 Risk scenario 3

Risk source	GM RSV
Causal pathway	Unintentional release of the GMO during storage or transport ⬇ Exposure of people or animals to the GMO ⬇ Transduction of cells ⬇ Establishment of viral infection
Potential harm	RSV disease in humans or animals

Risk source

148. The source of potential harm for this postulated risk scenario is GM RSV.

Causal pathway

149. Staff working at clinical trial or storage sites (who may or may not be involved in the dealings), external service providers (such as couriers) and people or animals in the wider environment, may come into contact with the GMO due to a spill during transport or storage.

150. The GMO will be supplied for import in small volumes, frozen and double-contained. Sealed vials (the primary container) will be separated by absorbent material and further sealed in a polybag (secondary container). The double-packaging, absorbent material and frozen nature of the GMO minimise the possibility that GMO leakage could contaminate the outer packaging. Nonetheless, the outer packaging will be labelled with instructions describing appropriate spill clean-up procedures, required PPE and disposal methods.

151. Commercial courier companies that are highly experienced with transport requirements for GMOs and infectious organisms, internationally and within Australia (e.g. World Courier), will import and transport the GMO, as well as export samples collected from trial participants. Packaging and transport of the GMO will be in accordance with IATA Dangerous Goods Regulations for shipping classification UN 3373 (Biological Substance, Category B) and, within Australia, the *Australian Code for the Transport of Dangerous Goods by Road & Rail* (National Transport Commission, 2017).

152. Storage of the GMO before distribution to individual clinical trial sites will be at a secure storage/distribution centre, such as Cryosite. Once at a clinical trial site, the GMO will be stored in the pharmacy in a secure freezer, with access restricted to pharmacy and clinical staff. All GMO stocks will be accounted for at each step through to destruction, and any unused GMO will be destroyed when the study is complete.

153. All storage and transport within clinical trial sites and off-site within Australia will be in accordance with the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*.

Potential harm

154. As described in earlier scenarios, the GMO is expected to be attenuated in humans and expected to result in disease no worse than that caused by the wild-type virus. As previously discussed, this applies equally to healthy individuals and any at-risk persons who may come into contact with the GMO.

155. As discussed in Chapter 1, RSV only infects humans and some non-human primates in the natural environment. Various non-primate animal species are semi-permissive to RSV infection and viral replication, and can be experimentally infected; these include cotton rats, mice, ferrets, guinea pigs, hamsters, chinchillas and lambs (Taylor, 2017). However, there are no reports of RSV infection or disease in these species in the natural environment. RSV infection and respiratory disease has been reported in wild gorillas and chimpanzees in Africa (Kondgen et al., 2008; Grutzmacher et al., 2016), however these apes are not present in the natural Australian environment.

156. RSV host range is determined by the non-structural proteins NS1 and NS2 (Bossert and Conzelmann, 2002). These genes have not been modified in the GMO, thus the GMO is expected to display the same host range as the wild-type virus.

157. Experimental infection of animals has often required large doses of RSV, particularly relative to their small size (Le Nouen et al., 2017; Taylor, 2017). Inadvertent exposure of susceptible non-primates is likely to involve a much lower quantity of the GMO than the infective dose of wild-type RSV.

158. Animals experimentally infected with RSV exhibit few, if any, signs of disease or pulmonary pathology (Taylor, 2017). In mice and hamsters inoculated with the GMO, a lower proportion of animals became infected, and viral replication was reduced in these animals, compared to those inoculated with wild-type rRSV (Le Nouen et al., 2017). Should a susceptible animal become infected with the GMO, the expected result is attenuated viral replication and little or no sign of disease.

Conclusion

159. Risk scenario 3 is not identified as a substantive risk because the potential for exposure will be minimised by appropriate packaging and containment during transport and storage, and ensuring all GMO stocks are accounted for and disposed of at the end of the study. The GMO is expected to cause less severe disease in people or animals than the wild-type virus. Therefore, this risk could not be greater than negligible and does not warrant further detailed assessment.

2.1.4 Risk scenario 4

Risk source	GM RSV
Causal pathway	Inoculation of trial participant with the GMO ⬇ Samples containing GMO collected, transported and analysed ⬇ Exposure of collection staff, couriers or laboratory staff ⬇ Transduction of cells ⬇ Establishment of viral infection
Potential harm	RSV disease

Risk source

160. The source of potential harm for this postulated risk scenario is GM RSV.

Causal pathway

161. Blood and urine samples, which may contain the GMO, will be taken from participants at yet to be determined times after inoculation with the GMO. As discussed in Chapter 1, there is some evidence of viraemia during RSV infection in neonates but it is unknown if viraemia also occurs in adults (Rohwedder et al., 1998). RSV was not detected in the blood or urine of hospitalised RSV-infected infants (von Linstow et al., 2006). Should samples contain the GMO, staff collecting and analysing these samples, and couriers involved in transport, may be inadvertently exposed.

162. Collection will take place at the clinical trial sites. Laboratories analysing samples from participants are yet to be identified but samples may be analysed by the testing laboratory at the same site, conducted off-site by external service providers such as pathology or contract laboratories (which may be certified as PC2 facilities by the Regulator), or may be exported. Thus patient samples from clinical sites may require couriered transport within Australia and for export.

163. Blood and urine samples transported from the collection area to the testing laboratory within the clinical trial site will be in double containment, with an accompanying pathology form indicating it contains a GMO with contact details of the applicant.

164. For off-site transport by road, samples will be packaged in accordance with the *Australian Code for the Transport of Dangerous Goods by Road & Rail* (National Transport Commission, 2017) for infectious substances. Export of samples will be packaged in accordance with IATA shipping classification UN 3373 (Biological Substance, Category B). This will minimise the likelihood of unintentional release of the GMO during transport.

165. In the event that samples leak beyond the secondary container during transport, the outer container will be labelled with instructions to contact the licence holder in the event of a spill, and warning text describing appropriate spill clean-up procedures, required PPE and disposal methods. These measures will minimise the likelihood that couriers would be exposed to the GMO if a spill occurs.

166. Certified PC2 facilities must comply with the Regulator's *Guidelines for Certification of a Physical Containment Level 2* as stated in the certification instrument.

167. Pathology laboratories must meet specified quality standards to be accredited. The *Health Insurance (Accredited Pathology Laboratories – Approval) Principles 2002* set out the specifics of pathology accreditation and its requirements. The standards developed by NPAAC include safety precautions to protect the safety of workers from exposure to infectious microorganisms in pathology laboratories.

168. Safe work practices in these laboratories must comply with the requirements of the *Work Health and Safety Act 2011* (Commonwealth) and state legislation related to work health and safety. Laboratories also follow the Australia/New Zealand 2243.3:2010 *Safety in laboratories Part 3: Microbiological safety and containment* (Standards Australia/New Zealand, 2010). This Standard sets out the requirements, responsibilities and general guidelines relating to safe handling and containment of microorganisms. It stipulates that human samples be handled in PC2 containment as a minimum standard.

Potential harm

169. As described in Risk Scenario 1, the GMO is expected to be attenuated in humans and expected to result in disease no worse than that caused by the wild-type virus. As discussed above, this applies equally to healthy staff and any at-risk individuals who may handle the GMO.

Conclusion

170. Risk scenario 4 is not identified as a substantive risk because exposure will be minimised by the double containment of samples during transport, and the legislation, standards and guidelines followed by pathology laboratories and other testing laboratories for specimens containing infectious

microorganisms. As for previous scenarios, the GMO is expected to cause less severe disease than the wild-type virus. Therefore, this risk could not be greater than negligible and does not warrant further detailed assessment.

2.1.5 Risk scenario 5

Risk source	GM RSV
Causal pathway	Inoculation of trial participant with the GMO ⬇ Trial participant sheds the GMO e.g. via respiratory secretions, sweat, saliva ⬇ Exposure of other people (e.g. household contacts or patients in clinical trial sites, including at-risk people and pregnant women) or animals via: i. direct contact with trial participant; ii. exposure to aerosolised secretions (e.g. from sneezing); or iii. contact with contaminated items (e.g. items the trial participant has touched, or contaminated tissues/waste); ⬇ Transduction of cells ⬇ Establishment of viral infection
Potential harm	Increased disease burden in humans or animals

Risk source

171. The source of potential harm for this postulated risk scenario is GM RSV.

Causal pathway

172. Once inoculated with GM RSV, participants will be permitted to leave the clinical site, and may shed the GMO into the environment. As discussed in Chapter 1, healthy adults infected with wild-type RSV typically shed the virus for 9-10 days, with peak shedding occurring 5 days post-inoculation (Falsey et al., 2003; Lee et al., 2004). Non-human primates infected with the MinL RSV shed it for a shorter duration of up to 5 days post-infection and the titres were 1000-fold lower than wild-type virus (Le Nouen et al., 2014). Given the expected attenuation of GM RSV, it is likely to replicate to lower titres than wild-type RSV in healthy adults, and shed in reduced quantities and/or for a shorter period. Despite current uncertainty as to the degree of attenuation in humans, shedding is not expected to exceed that of wild-type RSV.

173. Once trial participants return home, household contacts such as family members, domestic pets or livestock could be exposed to the shed virus, as could people in the wider environment, such as people working at or receiving treatment at the clinical trial site, work colleagues and fellow travellers on public transport. These people who come into contact with trial participants may include pregnant women or people at risk of severe RSV infection (e.g. young children, elderly, immunodeficient or immunosuppressed persons). People or animals could be exposed to the GMO through direct contact with the participant, exposure to aerosolised secretions (e.g. from sneezing), or contact with fomites (e.g. items contaminated by the participant such as used tissues, door handles or household items).

174. The applicant proposed that participants vaccinated with the GMO would be instructed to follow standard hygiene practices intended to minimise interpersonal spread of respiratory pathogens for a period of ten days following inoculation (see Chapter 1, paragraph 30). They will also be

instructed to seal soiled tissues and other materials used to collect respiratory secretions inside a primary container (a sealable plastic bag), place these in a secondary container provided by the clinical site, and store this in a place inaccessible to children and animals before returning it to the clinic for disposal as clinical waste. These practices will be explained to participants during initial screening and documented in the PIICF to which participants must agree before being enrolled in the trial. Compliance with these measures would limit the opportunity for other people and animals to come into contact with infectious secretions or items contaminated by trial participants during the period of peak viral shedding.

175. The applicant also proposed that participants would be instructed not to care for immunosuppressed or immunodeficient persons and to avoid contact with such persons for at least ten days after inoculation. The applicant also expects that participants would be instructed to avoid pregnant women after inoculation. These measures will minimise the opportunity for participants to transmit the GMO to people at higher risk of developing severe RSV disease.

176. Additionally, the environmental stability of RSV is low, losing viability in minutes to several days at room temperature (Pirtle and Beran, 1991; Canada, 2011).

Potential harm

177. As the GMO is expected to be attenuated in humans, it is likely that it would not replicate to high titres in healthy trial participants. Therefore, the amount of virus shed in various secretions is expected to be less than the dose administered to the participant, and less than that shed during an infection with wild-type RSV. Any person inadvertently exposed to the GMO would thus receive a much lower dose than that administered to the participant.

178. As described in Chapter 1, there is some evidence to suggest that vertical transmission of RSV is possible. Transplacental transmission has been demonstrated in rats, although no abnormal histology was observed in the foetal and newborn lungs and airways (Piedimonte et al., 2013). RSV has been detected in human cord blood (Fonceca et al., 2017), and RSV may have been transmitted to an unborn child by a mother infected with RSV during pregnancy (Manti et al., 2017). The newborn experienced viral pneumonia and required neonatal intensive care.

179. RSV is endemic in Australia, affecting thousands of adults, newborns and infants annually (Roche et al., 2003). As discussed previously, given its expected attenuation in humans, even an infective dose of the GMO would not produce disease worse than that caused by wild-type RSV in either healthy or at-risk categories of people.

180. As discussed in risk scenario 3, attenuation in animals has been demonstrated and the genetic modifications are not expected to alter the host range of the GMO. Thus any low dose to which non-primates may be exposed is not likely to lead to infection or disease.

Conclusion

181. Risk scenario 5 is not identified as a substantive risk because the potential for exposure of other people or animals will be minimised by proposed hygiene and waste disposal measures to be undertaken by trial participants, the limited quantity of GMO they are likely to shed, and instructing trial participants to avoid contact with at-risk people after inoculation. As for previous scenarios, the GMO is expected to cause less severe disease than the wild-type virus. Therefore, this risk could not be greater than negligible and does not warrant further detailed assessment.

2.1.6 Risk scenario 6

Risk source	GM RSV
Causal pathway	Inoculation of trial participant with the GMO ⬇ Donation of blood, blood products, organs or tissues containing the GMO ⬇ Transduction of cells in recipient ⬇ Establishment of viral infection
Potential harm	RSV disease

Risk source

182. The source of potential harm for this postulated risk scenario is GM RSV.

Causal pathway

183. Should a participant donate blood, blood products, organs or tissues after inoculation with the GMO, GM RSV may be present in the donated product and the recipient may become infected.

184. Before being enrolled in the study, trial participants will agree not to donate blood, tissues or organs for the duration of the study, and not to donate blood and blood products for a further 6 months after the study is complete. This will minimise the likelihood that human biological materials containing GM RSV will be transferred to other people.

185. As discussed in Chapter 1, however, RSV can persist at a low level of viral replication for long periods, for example in human bone marrow, myocardium and liver (Eisenhut, 2006; Rezaee et al., 2011). It is therefore theoretically possible for the GMO to persist long-term in the body of a trial participant who becomes a blood or tissue donor at a later time.

186. As discussed in risk scenario 5, replication of the GMO in healthy trial participants is expected to be reduced relative to that of the wild-type virus. Therefore, circulating viral titres are expected to be low and decline over time due to immune clearance. This may restrict occurrence of persistent viral infection.

Potential harm

187. RSV infection is common in the Australian population, and the wild-type RSV would therefore occasionally be present in blood, tissue and organ donations. Any disease arising in a recipient of such materials from a current or former trial participant is not expected to experience worse disease than that due to wild-type virus acquired by the same route.

Conclusion

188. Risk scenario 6 is not identified as a substantive risk because the potential for recipients of donated human biological materials to be exposed to GMO RSV will be minimised by only enrolling participants who agree not to donate blood, blood products, organs or tissues for a period after inoculation with the GMO, and any resulting disease is expected to be less severe than that arising from wild-type RSV, which would be transmitted via blood and organ donation from time to time. Therefore, this risk could not be greater than negligible and does not warrant further detailed assessment.

2.1.7 Risk scenario 7

Risk source	GM RSV
Causal pathway	Inoculation of trial participant with the GMO ⬇ Trial participant is already, or later becomes, infected with wild-type RSV or other *Pneumoviridae* species ⬇ Co-infection of host cells ⬇ Recombination between GM and wild-type viral genomes takes place ⬇ Novel recombinant virus infects other hosts
Potential harm	Increased disease burden due to novel virus with altered virulence

Risk source

189. The source of potential harm for this postulated risk scenario is GM RSV.

Causal pathway

190. There is potential for recombination between GM RSV and a circulating wild-type RSV strain or another species of the *Pneumoviridae* family if a trial participant is infected with such a virus at the time of inoculation, or becomes infected shortly afterwards.

191. For recombination to occur, the GMO and a second virus must co-infect the same host cell. However, co-infection of a single cell by two different RSV strains is uncommon.

192. As discussed in Chapter 1, recombination between single-stranded RNA viruses is considered rare. Recombination between RSV strains or other species of *Pneumoviridae* family in the natural environment has not been documented. Recombination has been achieved experimentally by co-infecting two RSV strains into cultured cells but occurred only at a low frequency (Spann et al., 2003). The mutations introduced into the GMO would reduce the level of homology with other RSV strains, and therefore further reduce the likelihood of homologous recombination.

193. *Human metapneumovirus* causes respiratory disease in humans and, along with wild-type RSV, is a potential recombination partner for GM RSV. As discussed in Chapter 1, annual epidemics of RSV infections occur during winter and spring in temperate regions of Australia, and in adults with "influenza-like" symptoms, RSV is detected at a rate of only 3.1%. *Human metapneumovirus* is found at a rate of 3.4% (Varghese et al., 2018). Given that a maximum of 350 people will receive the GMO, only a small number are likely to experience co-infection with either wild-type RSV or *human metapneumovirus.*

194. Furthermore, *human metapneumovirus* lacks the NS1 and NS2 genes found in RSV, has a different gene order and belongs to different genus (van den Hoogen et al., 2002; Tripp, 2009). It is thus unlikely that the GMO and *human metapneumovirus* would recombine. There are no reports of recombination between these two viral species.

Potential harm

195. Should the GMO recombine with a circulating wild-type RSV, the resulting recombinant could have any permutation of genomic regions of the two parental strains. As discussed in Chapter 1, the MinL RSV was shown to be attenuated compared with the wild-type rRSV and the additional amino acid mutations further attenuated the MinL RSV. Any novel viral progeny carrying mutations from the GMO is not expected to display increased pathogenicity or virulence compared with the wild-type parent, rather it is likely to retain the attenuated phenotype associated with those particular

mutations. Thus, the likely outcome of recombination between the GMO and another RSV strain is likely to be a virus of similar or lower virulence than the wild-type virus already circulating in the environment.

Conclusion

196. Risk scenario 7 is not identified as a substantive risk because recombination is uncommon and has not been documented in the natural environment, and any novel virus resulting from recombination between the GMO and a wild-type RSV strain is not expected to be more pathogenic or virulent than the circulating wild-type virus. Therefore, this risk could not be greater than negligible and does not warrant further detailed assessment.

2.1.8 Risk scenario 8

Risk source	GM RSV
Causal pathway	Inoculation of trial participant with the GMO ⬇ Exposure of other people by pathways described in scenarios 1-6 ⬇ Altered characteristics of the GMO in the host ⬇ Unintended host reaction
Potential harm	Toxicity, allergenicity or abnormal immune response

Risk source

197. The source of potential harm for this postulated risk scenario is GM RSV.

Causal pathway

198. Neither the CPD of the L gene nor the deletion in non-coding sequences from the SH gene alter the encoded amino acid sequences, therefore these modifications would not directly lead to altered toxicity, allergenicity or immune response but do affect viral gene expression. The other modifications each produce only a single amino acid change in one of the encoded N, P, M2-1 and L proteins. The effect of the amino acid changes in these proteins may be altered protein activity or interaction with other viral proteins or host cell molecules. These changes could result in unexpected effects such as a toxic or allergic response or altered immune response in people exposed to the GMO.

199. Exposure pathways are described above in scenarios 1-6.

Potential harm

200. A single amino acid change in a viral protein is not expected to create a toxin, as the protein would remain highly similar to the wild-type protein. In animal studies, the GMO displayed a greatly attenuated phenotype. In mice and hamsters inoculated with the GMO, fewer individual animals became infected compared to those inoculated with wild-type RSV, and viral replication was reduced in lungs and nasal turbinates of those that did become infected. Hamsters inoculated with the GMO were protected from later infection by wild-type RSV. No unexpected effects were reported in these studies (Le Nouen et al., 2017).

201. In a clinical trial with live attenuated RSV vaccines containing missense mutations in the N, L and F genes, between 7-77% of inoculated children experienced upper respiratory disease, but no toxic or allergic reactions were reported (Whitehead et al., 1999; Karron et al., 2005). In a clinical trial involving young children vaccinated with another live attenuated RSV vaccine, containing a number of

silent and missense nucleotide mutations in the RSV genome (known as MEDI-559), there was one case of bronchiolitis requiring hospitalisation of a child (Malkin et al., 2013). These studies reported antibody responses and protective immunity against the virus, and no abnormal immune responses were observed (Karron et al., 2005; Malkin et al., 2013). For these RSV vaccines, the degree of attenuation appears to have been an issue, rather than unintended effects of the modifications.

202. Therefore, the GMO is not expected to cause toxicity, allergenicity or an abnormal immune response in people.

Conclusion

203. Risk scenario 8 is not identified as a substantive risk because studies of the GMO in animals have not shown any unintended effects, and clinical trials with similar RSV vaccines have not shown any indication of toxicity, allergenicity or abnormal immune response. Therefore, this risk could not be greater than negligible and does not warrant further detailed assessment.

Section 3 Uncertainty

204. Uncertainty is an intrinsic property of risk analysis and is present in all aspects of risk analysis[1].

205. There are several types of uncertainty in risk analysis (Clark and Brinkley, 2001; Hayes, 2004; Bammer and Smithson, 2008). These include:

- uncertainty about facts:
  - knowledge – data gaps, errors, small sample size, use of surrogate data
  - variability – inherent fluctuations or differences over time, space or group, associated with diversity and heterogeneity
- uncertainty about ideas:
  - description – expression of ideas with symbols, language or models can be subject to vagueness, ambiguity, context dependence, indeterminacy or under-specificity
  - perception – processing and interpreting risk is shaped by our mental processes and social/cultural circumstances, which vary between individuals and over time.

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

207. As clinical trials of GM therapeutics are designed to gather data, there are generally data gaps when assessing the risks associated with such applications. This is one reason they are required to be conducted under specific limits and controls. Even if there is uncertainty about the characteristics of a GMO, these limits and controls restrict exposure to the GMO and thus decrease the likelihood of harm.

208. For DIR 161, uncertainty is noted particularly in relation to:

- the degree of attenuation of the GMO in humans relative to unmodified RSV, particularly in those at risk of developing severe RSV disease, such as immunosuppressed individuals;
- the minimum infectious dose of the GMO relative to that of unmodified RSV; and
- the extent and period of shedding of infectious GMO particles by trial participants.

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

209. These areas of uncertainty have been addressed in the risk assessment by conservative assumptions including allowing for the possibility that attenuation of the GMO in people is less than that observed in animal models, and assuming that the GMO shed by trial participants would be sufficient to infect other people. After taking this uncertainty into account all risk scenarios were estimated to represent negligible risk.

210. Additional data, including information to address these uncertainties, may be required to assess possible future applications with reduced limits and controls, such as commercial release of the GMO.

211. Chapter 3, Section 4, discusses information that may be required for future release.

Section 4 Risk evaluation

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

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

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

214. Eight risk scenarios were postulated whereby the proposed dealings might give rise to harm to people or the environment. In the context of the limits and controls proposed by the applicant, and considering both the short and long term, none of these scenarios were identified as substantive risks. The principal reasons for these conclusions are summarised in Table 2 and include:

- standard procedures followed by clinical trial staff in handling, administering and disposing of infectious material
- limits and controls proposed by the applicant for transporting, storing, preparing and administering the GMO
- procedures to be followed by trial participants to minimise the spread and transmission of the GMO
- any disease resulting from the GMO in humans is expected to be less severe than that caused by unmodified RSV, which is widespread in the environment.

215. Therefore, risks to the health and safety of people, or the environment, from the proposed clinical trial of GM RSV into the environment are considered to be negligible. The *Risk Analysis Framework* (OGTR 2013), which guides the risk assessment and risk management process, defines negligible risks as risks of no discernible concern with no present need to invoke actions for mitigation. Therefore, no additional controls are required to treat these negligible risks. Hence, 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 plan

Section 1 Background

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

217. 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.

218. 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.

219. 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.

Section 2 Risk treatment measures for substantive risks

220. The risk assessment of risk scenarios listed in Chapter 2 concluded that there are negligible risks to people and the environment from the proposed clinical trials of the GMO. These risk scenarios were considered in the context of the limits and controls proposed in the application (Chapter 1, Section 2.3), the parent organism (Chapter 1, Section 3), the GMO (Chapter 1, Section 4), and considering both the short and the long term. The risk evaluation concluded that no specific risk treatment measures are required to treat these negligible risks. Limits and controls proposed by the applicant and other general risk management measures are discussed below.

Section 3 General risk management

221. The limits and controls proposed in the application were important in establishing the context for the risk assessment and in reaching the conclusion that the risks posed to people and the environment are negligible. Therefore, to maintain the risk context, licence conditions have been imposed to limit the release to the proposed size, location and duration, and to restrict the spread and persistence of the GMOs and their genetic material in the environment. The conditions are discussed and summarised in this Chapter and listed in detail in the licence.

3.1 Licence conditions to limit and control the release

3.1.1 Consideration of limits and controls proposed by CNS Pty Ltd

222. Chapter 1 provides details of the limits and controls proposed by CNS Pty Ltd in their application. These are taken into account in the eight risk scenarios postulated for the proposed release in Chapter 2. The appropriateness of these limits and controls is considered further below.

223. The applicant proposed that clinical trials will be conducted at clinical trial sites, and the duration of the trials will be limited to five years. The applicant proposed inoculating up to 350 healthy adults of both genders. Inoculation of trial participants and collection of samples will be conducted at clinical trial sites. These limits will minimise the potential exposure of people and other organisms to the GMO, and are included in the licence.

224. Clinical trial sites have institutional policies and procedures based on 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 in the clinical setting. Samples from trial participants, which may contain the GMO, may be analysed at analytical facilities including pathology laboratories and contract laboratories, such as PC2 facilities certified by the Regulator. These analytical facilities follow relevant guidelines that minimise staff exposure to infectious microorganisms and maintain containment of microorganisms (Risk scenario 4). As the GMO would be present at low level in such samples, and are expected to be attenuated, these standard measures are considered appropriate. Therefore no additional conditions are included in the licence relating to participant samples. Licence conditions are included that require the licence holder to ensure that dealings, other than import and transport by external service providers, are conducted in clinical trial sites and analytical facilities which employ appropriate work practices and adhere to relevant standards.

225. The applicant proposed that only suitably qualified and trained staff will be permitted to deal with the GMO. The GMO will only be prepared and administered by suitably trained and qualified staff associated with the clinical trial. The applicant proposed that clinical trial staff preparing the GMO will wear PPE including a long-sleeved laboratory coat or gown and gloves. The GMO for inoculation will be prepared in a Class II BSC. No sharps will be used when preparing the GMO. The GMO will be administered to trial participants by intranasal spray which may expose clinical trial staff to aerosols containing the GMO. Clinical trial staff administering the GMO to trial participants will wear PPE including laboratory coat or gown, gloves, eye protection and a mask protecting the nose and mouth. Clinical trial staff, who are pregnant or have an immunodeficiency or immunosuppression, will be excluded from handling or administering the GMO (Risk scenario 1). Only the trial participant and two clinical staff will be in the room during administration. These measures will minimise exposure of people conducting dealings at clinical trial sites to the GMO, including those at risk of experiencing severe RSV disease, and are included in the licence conditions. Licence conditions also include educating staff handling the GMO, dispensing the GMO, administering it to trial participants or caring for trial participants on the potential for transmission of the GMO to people who are at risk of severe RSV infection including children aged 2 years or younger, and the elderly.

226. The GMO will be administered to healthy adults only. People at increased risk of severe RSV disease, being children aged 2 years or younger, people with an immunodeficiency, immunosuppression or other risk factors (e.g. cardiovascular or pulmonary disorders), will be excluded from participating in the clinical trials. Women who are pregnant, planning to become pregnant or breastfeeding, may transmit the GMO to their foetus or baby, and will also be excluded from participating in the clinical trials. This will minimise the potential shedding and transmission of the GMO by trial participants suffering severe RSV disease (Risk scenario 5). A licence condition has been imposed requiring participants to be instructed to avoid contact with at-risk groups including children aged 2 years or younger, and residents of aged care facilities, in addition to immunodeficient/ immunosuppressed persons and pregnant women. Persons unwilling or unable to comply with the instructions will be excluded from participating in the study. These measures will minimise the exposure of people who are at increased risk of severe RSV disease to the GMO.

227. Trial participants will be instructed to implement hygiene measures to prevent interpersonal transmission of the GMO including respiratory and cough etiquette. The applicant proposed that they will be instructed to seal tissues and other materials used to collect respiratory secretions in double containers provided by the clinical trial site for 10 days after inoculation of the GMO, and return these to the clinical trial site for disposal. Licence conditions have been imposed that trial participants must

agree to follow hygiene measures, avoid contact with at-risk groups and collect contaminated waste in containers for a period of 14 days after inoculation instead of 10 days. Given that this is a first-in-human clinical trial of the GMO and there is no direct data on GMO shedding by humans, this additional precaution is imposed to minimise the potential for transmission of the GMO in the event that GMO shedding lasts longer than anticipated. Waste containers are to be kept away from children and animals (Risk scenario 5). Participants will be instructed to refrain from donating blood, blood products, tissues or organs from the time of their first inoculation with the GMO until 6 months after their final inoculation (Risk scenario 6). They will be educated about the potential for transmission of the GMO to other people including those who are at risk of severe RSV infection, including children aged 2 years or younger, and the elderly. This information must be included in the PIICF to be signed by participants. These measures will minimise the exposure of other people and animals in the environment to the GMO.

228. The GMO will be imported and transported within Australia according to the requirements of the IATA Dangerous Goods Regulations for shipping classification UN 3373 (Biological Substance, Category B), the *Australian Code for the Transport of Dangerous Goods by Road & Rail* (National Transport Commission, 2017) and the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* (Risk scenario 3). Imported GMO will be stored at secured storage/distribution centres in Australia, also in accordance with the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*, before distribution to clinical trial sites. These transport and storage measures will minimise exposure of people and animals to the GMO. Licence conditions include import and transport of the GMO to be in accordance with the relevant IATA requirements, or the transport requirements for PC2 GMOs of the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*, and storage of the GMO to be in accordance with the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*.

229. At clinical trial sites, all unused GMOs and any materials contaminated with the GMO, including soiled tissues and waste collected from trial participants, will be disposed of as infectious clinical waste in accordance with the institutional procedures and state legislation for the disposal of infectious clinical waste (Risk scenario 2). The applicant has stated that incineration of waste is likely, but decontamination by steam sterilisation or chemical treatment is also possible. All three methods are considered appropriate for disposal of clinical waste containing the GMO, and will minimise exposure of people and animals to the GMO. The licence requires that all waste must be disposed of as infectious clinical waste.

230. Maintaining records of all GMOs received, dispensed and destroyed will ensure all vials of the GMOs and waste collected from trial participants are accounted for. Destroying all GMOs remaining when inoculation of all trial participants is complete will ensure it is not inadvertently released at a later time. These practices have been included as licence conditions.

3.1.2 Summary of licence conditions to be implemented to limit and control the release

231. A number of licence conditions have been imposed to limit and control the release, based on the above considerations. These include requirements to:

- limit the release from the date of licence issue to July 2023
- limit the inoculation to up to 350 healthy adults by intranasal spray
- administer the GMO and collect samples from trial participants at clinical trial sites
- conduct dealings, other than import and transport carried out by external service providers, at facilities that employ appropriate work practices and adhere to relevant standards
- exclude clinical trial staff who are pregnant, or have an immunodeficiency or immunosuppression, from handling or administering the GMO
- instruct trial participants in measures to minimise the potential for transmission of the GMO to other people

- not administer the GMO to: women who are pregnant, breastfeeding or not willing to use effective contraception while participating in the study; children; persons who care for children aged 2 years or younger; residents of aged care facilities; persons who have an immunodeficiency, immunosuppression or other risk factors for more severe clinical RSV disease; or anyone unwilling or unable to comply with the instructions described in the licence
- transport and store the GMO in accordance with the relevant IATA requirements, or the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*, in force at the time.

3.2 Other risk management considerations

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

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

3.2.1 Applicant suitability

233. 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, for either an individual applicant or a body corporate, include:

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

234. The licence includes a requirement for the licence holder to inform the Regulator of any new information that would affect their suitability.

235. 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 plan

236. CNS Pty Ltd is required to submit a contingency plan to the Regulator before commencing dealings with the GMOs. This plan would detail measures to be undertaken in the event of an unintentional release of the GMO such as a spill, suspected or confirmed transmission of the GMO to people other than trial participants, or a person developing a serious adverse event which may be related to exposure to the GMO, including those known to result from infection with RSV.

237. CNS Pty Ltd is also required to provide the Regulator with a methodology to reliably detect the GMO, and the presence of the genetic modifications in a recipient organism, and which is able to distinguish between the GMO and the unmodified parent organism. This methodology would be required before commencing dealings with the GMO.

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

238. The persons covered by the licence are 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 dealing with the GMO, CNS Pty Ltd is required to provide a list of people and

organisations that would be covered by the licence, or the function or position where names are not known at the time.

3.2.4 Reporting requirements

239. The licence requires the licence holder to immediately report any of the following to the Regulator:

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

240. A number of written notices are also required under the licence regarding dealings with the GMO at each Clinical Trial Site, to assist the Regulator in designing and implementing a monitoring program for all licensed dealings. The notices include:

- the names of all organisations and persons (other than trial participants), or functions or positions of persons, who will be covered by the licence at that Clinical Trial Site, with a description of their responsibilities
- details of how persons covered by the licence will be informed of licence conditions
- details of each Clinical Trial Site, and the first and last inoculation at each site
- details of how the licence holder will ensure compliance with licence conditions at the Clinical Trial Site over the period that dealings are conducted at that location.

3.2.5 Monitoring for compliance

241. 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. Post-release monitoring continues until the Regulator is satisfied that all the GMOs resulting from the authorised dealings have been removed from the release site.

242. 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.

243. 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 Issues to be addressed for future releases

244. Additional information has been identified that may be required to assess an application for a commercial release of this GMO or to justify a reduction in limits and controls. This includes:

- additional information on the virulence, transmission and shedding characteristics of the GMO in people
- information on any adverse events or clinical symptoms that may be associated with inoculation of the GMO.

Section 5 Conclusions of the RARMP

245. The RARMP concludes that the proposed limited and controlled release of the GMO poses negligible risks to the health and safety of people or the environment as a result of gene technology, and that these negligible risks do not require specific risk treatment measures.

Conditions have been imposed to limit the release to the proposed size, location 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.

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Appendix A Summary of submissions from prescribed experts, agencies and authorities[2]

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 currently available scientific evidence and were used in finalising the RARMP that formed the basis of the Regulator's decision to issue the licence.

Sub. No.	Summary of issues raised	Comment
1	The Committee agrees with instructions in relation to blood and organ donation.	Noted.
	Consider clarifying trial exclusion on the basis of immunodeficiency, age and pregnancy.	A licence condition is imposed that the exclusion criteria include women who are pregnant, and persons with immunodeficiency or immunosuppression. Given that the clinical trial would include elderly people, no upper age restrictions are imposed, however a condition has been added to exclude residents of aged care facilities from participating in the trials as they are likely to be in close contact with at-risk people.
	Further consider controls around the numbers of trial participants.	The maximum number (350) of trial participants to be inoculated with the GMO is less than that imposed for a similar codon deoptimised GM vaccine against influenza for DIR 144 (500 trial participants). Given that the GMO is attenuated and licence conditions have been imposed to limit the spread of the GMO to other at-risk groups, further limiting the number of trial participants is not warranted. Furthermore, the licence holder is required to immediately report any adverse effects and therefore the trial could be stopped if there are health concerns.
	Further consider attenuation of the GMO and risks related to transmission.	Attenuation of the GMO has been demonstrated by the reduced replication *in vivo* compared with the wild-type virus attenuated in the RARMP (Ch.1 Sec. 4.2). Risk scenario 5 considers the risks associated with shedding of the GMO by trial participants, leading to infection of other people. This scenario takes into account exposure to the GMO via various routes. Conditions requiring the licence holder to educate clinical trial staff and participants about transmission to people with increased risk of severe RSV infection will contribute to minimising the exposure of at-risk people to the GMO.
	Consider clarifying potential symptoms that may be associated with the GMO.	As the GMO is attenuated, if a trial participant experiences symptoms after GMO inoculation, it is likely that the symptoms would be similar to but less severe than those associated with wild-type RSV infection. Further information on clinical symptoms associated with the GMO exposure is not required for management of risks from the proposed trials, however

[2] 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	Comment
		Ch. 3 of the RARMP notes that such information may be required to assess an application for a commercial release of this GMO or to justify a reduction in limits and controls.
	Consider the impact of mutations, other than codon deoptimisation, on attenuation of the GMO.	The impact of the mutations has been described in Ch. 1, Sec. 4, and Ch. 2, Risk Scenarios 1 and 8. No other effects have been identified. Ch. 3 of the RARMP notes that further information on the symptoms associated with GMO exposure may be required to assess an application for a commercial release of this GMO or to justify a reduction in limits and controls.
2	No major concerns regarding the RARMP. The postulated risk scenarios and the assessment of these scenarios in the context of the limits and controls to be imposed are acceptable.	Noted.
	The clinical trial sites where the GMO would be administered may also have immunocompromised patients participating in other studies, and who may be environmentally exposed to the GMO aerosol.	Risk scenario 5 considers transmission to other at-risk people within or outside the clinical trial sites. Licence conditions have been included that requires the licence holder to educate clinical trial staff and trial participants of the potential for transmission of the GMO to people who are at risk of severe RSV infection. An additional condition has been imposed that only the trial participant and two clinical staff will be in the room during administration, as proposed in the application.
	Consideration should be given to whether participants or workers who are in close contact with children < 1 year should be involved. Or at least these people should be warned of the potential spread to young children and consequences.	Licence conditions have been included that require the licence holder to educate clinical trial staff and trial participants on the potential for transmission of the GMO to people who are at risk of severe RSV infection, including young children.
	The proposed GMO was tested for genetic stability, viral replication, immunogenicity, etc. but not the potential recombination with other RSV mutants or wild-type RSV.	Potential for recombination was considered in Risk scenario 7 and not considered a substantive risk. Recombination of RSV has not been documented in the natural environment.
	There was no information on pathogenicity of the GMO in non-human primates although the viral titres were lower than the wild-type.	MinL RSV, which contains most of the modifications present in the GMO, was tested in non-human primates (Ch. 1, Sec. 4.2). While the severity of the RSV disease, if any, was not reported, virus was shed for only half the duration, and was present at 1000-fold lower levels in analysed sample, compared to wild-type RSV
3	No concerns with the application.	Noted.
4	Agrees with the conclusion of the RARMP.	Noted.
	Additional references that may be useful were identified in relation to viruses closely related to RSV; host range of closely related viruses; and possible enhancement of RSV infection by co-infection with *Streptococcus pneumoniae* bacteria.	Consideration of these references has been included in the RARMP (Ch.1, Sec. 5), except for the study by Nguyen et al 2015 as the study does not indicate that co-infection of *S. pneumoniae* and RSV exacerbates RSV disease in humans.
5	The protocols have been well thought through, and the RARMP seems to be pretty comprehensive.	Noted.

Sub. No.	Summary of issues raised	Comment
	The main risk is associated with the potential for transmission from trial participants to the general population. The mechanism of reduction in replication is not known, nor is the replication level below which transmission is prevented. Has the shedding profile of the GMO been compared to the shedding profile of the parental virus in an animal model? If so were there any differences?	Codon pair deoptimisation of viral genes reduces viral replication by lowering the efficiency of translation in host cells (Ch. 1, Sec. 4.1). MinL RSV, which contains most of the modifications present in the GMO, was tested in non-human primates (Ch. 1, Sec. 4.2). Virus was shed for only half the duration, and was present at 1000-fold lower levels in analysed sample, compared to wild-type RSV.
	Trial participants are to be instructed to seal soiled tissues in a container for 10 days after inoculation with the GMO. The collection period should have a safety margin above the known shedding period for the wild-type RSV e.g. 15 or 20 days.	As discussed in the RARMP, healthy adults inoculated with RSV shed the virus for an average duration of 9-10 days post-inoculation (Ch.1, Sec. 3.5). The reduced ability of the GMO to replicate *in vivo* in animals suggests that the GMO is likely to be shed for a shorter duration and at lower levels than wild-type RSV. Nevertheless, a licence condition now specifies a period of 14 days, instead of 10 days, after each GMO inoculation for collection of waste as an additional precaution. Given that this is a first-in-human clinical trial and there is limited data on GMO shedding by humans, this precaution will minimise the potential for transmission of the GMO.
	RSV infection has been suggested as a possible risk factor for children later developing asthma. Will people likely to have close contact with infants or young children (<1 yr) be included in the trial? Similarly, given that the replication profile of the GMO is unknown in humans, will trial participants be instructed to avoid contact with older people who may have reduced immune function? These groups of the population may be more susceptible to RSV and potentially the GM RSV.	Licence conditions have been included that require the licence holder to educate clinical trial staff and trial participants of the potential for transmission of the GMO to people who are at risk of severe RSV infection, including young children. The licence holder must obtain written agreement from the trial participants that they will avoid contact with children aged 2 years or younger and residents of aged care facilities.
	Will the trial participants be tested long term for potential persistence of the GMO?	Testing long term persistence of the GMO in trial participants is not proposed. Due to its attenuation the GMO would likely be cleared by the immune system and not persist in healthy adult trial participants. However, any persistence would not present a risk greater than that from wild-type RSV, which is widespread in the Australian environment.
	Why is it not possible to have a set schedule of sampling and follow-up visits to the clinical trial site after inoculation?	The licence holder has not yet finalised the clinical trial protocol for the first-in-human trials.
6	Supported the OGTR's conclusion that DIR 161 poses negligible risk of harm to human health and safety and the environment.	Noted.
7	Supported the conclusion that the application has negligible risks to the health and safety of people and the environment. Satisfied that the measures taken to manage the short and long term risks of the application are adequate.	Noted.

No submissions have been received from members of the public.