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

December 2024

Risk Assessment and Risk Management Plan

(consultation version)

for

DIR 208 – Clinical trial of GM vaccinia virus for the treatment of solid tumours

Applicant – Novotech (Australia) Pty Limited

This RARMP is open for consultation until 30 January 2025.

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

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

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

Please note that issues regarding the patient's safety and the quality and efficacy of the treatment do **not** fall within the scope of these evaluations as they are the responsibilities of other agencies and authorities.

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Summary of the Risk Assessment and Risk Management Plan (Consultation Version)
for
Licence Application No. DIR 208

Introduction

The Gene Technology Regulator (the Regulator) has received a licence application to conduct a clinical trial using a genetically modified organism (GMO). It qualifies as a DIR licence application under the *Gene Technology Act 2000* (the Act).

The applicant, Novotech (Australia) Pty Limited (Novotech), proposes to conduct a clinical trial to evaluate the safety and efficacy of a genetically modified (GM) vaccinia virus (VACV), for the treatment of solid tumours.

The proposed GM VACV has been designed to preferentially replicate in, and kill cancer cells. The GM VACV would be manufactured overseas and imported into Australia. It would be administered by intravenous infusion in up to 40 patients with solid tumours at clinical facilities and hospitals in Australia.

Clinical trials in Australia are conducted in accordance with requirements of the *Therapeutic Goods Act 1989*, which is administered by the Therapeutic Goods Administration (TGA). Therefore, in addition to approval by the Regulator, Novotech would require authorisation from the TGA before the trial commences. Clinical trials conducted in Australia must also be conducted in accordance with the *National Statement on Ethical Conduct in Human Research* and with the *Guidelines for Good Clinical Practice* of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Novotech would also require approval from the Department of Agriculture, Fisheries and Forestry (DAFF) for import of the GMO into Australia. In addition, they may require approval from the Chief Inspector of Stock before bringing the GMO into South Australia; an authorisation from the Department of Jobs, Skills, Industry and Regions - Agriculture Victoria in Victoria and a Prohibited Matter Permit from New South Wales, Queensland and Western Australia if they wish to conduct dealings in those states.

The Regulator has prepared a Risk Assessment and Risk Management Plan (RARMP) for this application, which concludes that the proposed clinical trials pose negligible risks to human health and safety and the environment. Licence conditions have been drafted for the proposed clinical trial. The Regulator invites submissions on the RARMP, including draft licence conditions, to inform the decision on whether or not to issue a licence.

The application

Project Title	Clinical trial of GM vaccinia virus for the treatment of solid tumours
Parent organism	Vaccinia virus (VACV)
Principal purpose	The proposed trial is a Phase 1 study designed to evaluate the safety and efficacy of a genetically modified (GM) vaccinia virus, for the treatment of patients with solid tumours.
Genetic modifications	Introduced genes[1]: • Three separate genes related to immune function of human origin, which enhance anti-tumour immune responses. Deleted genes[1]: • The deletion of three VACV genes, which improves the efficacy and safety of the GMO.
Previous clinical trials	This is a first in human clinical trial using this GMO
Proposed limits and controls	
Proposed duration	5 years
Proposed number of participants	Up to 40 clinical trial participants in Australia
Proposed locations	The proposed trial would be conducted at a number of hospitals and clinics across Australia. The exact clinical trial sites are yet to be identified
Proposed controls	• Transport and storage of the GMO according to the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* • Require staff handling the GMO to be trained and to use personal protective equipment • Staff with immunosuppressive disorders are excluded from handling the GMO • Disposal of waste that may contain GMO according to clinical site procedures appropriate for risk group 2 organisms • Provide patients with detailed instructions regarding the care of any skin-related reactions post-treatment and the use of good hygiene practices

Risk assessment

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

Credible pathways to potential harm that were considered included the; potential exposure of people or animals to the GMO; and the potential for the GMO to transfer or acquire genetic material from

[1] Confidential Commercial Information (CCI): Some details about the inserted and deleted genes have been declared as CCI under section 185 of the Act. This information will be made available to the prescribed experts and agencies that will be consulted on this application. CCI is not available to the public.

other viruses. The potential for the GMO to be released into the environment and its effects were also considered.

The risk assessment concludes that the trial poses negligible risks to human health and safety and to the environment. No specific risk treatment measures are required to manage these negligible risks. Important factors in reaching the conclusions of the risk assessment included that the GM VACV treatment selectively replicates in cancer cells, and unintended exposure to the GMOs would be minimised by the limits and controls.

As risks to the health and safety of people, or the environment, from the proposed trial of the GMO treatment have been assessed as negligible, the Regulator considers that the dealings involved do not pose a significant risk to either people or the environment.

Risk management

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. Draft licence conditions are detailed in Chapter 4 of the RARMP.

As the level of risk is considered negligible, specific risk treatment is not required. However, since this is a clinical trial, the draft licence includes limits on the number of trial participants, types of facilities used, limits on the duration of the trial, as well as a range of 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.

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Abbreviations

°C	Degrees Celsius
CCI	Confidential Commercial Information
CDC	Centers for Disease Control and Prevention
DAFF	Department of Agriculture, Fisheries and Forestry
DIR	Dealings involving Intentional Release
DNA	Deoxyribonucleic acid
GM	Genetically modified
GMO	Genetically modified organism
kb	kilobase
HREC	Human Research Ethics Committee
IATA	International Air Transport Association
IBC	Institutional Biosafety Committee
ICH-GCP	*Guidelines for Good Clinical Practice* of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
i.v.	Intravenous
NLRD	Notifiable Low Risk Dealings
NYCBH	New York City Board of Health
OGTR	Office of the Gene Technology Regulator
OPV	*Orthopoxvirus*
pfu	pock-forming units; plaque forming units
PPE	Personal protective equipment
RARMP	Risk Assessment and Risk Management Plan
Regulations	Gene Technology Regulations 2001
Regulator	Gene Technology Regulator
TGA	Therapeutic Goods Administration
the Act	*Gene Technology Act 2000*
TSD	Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*
USA	United States of America
VACV	*Vaccinia virus*
VIG	Vaccinia immunoglobulin
WHO	World Health Organisation

Chapter 1 Risk assessment context

Section 1 Background

1. An application has been made under the *Gene Technology Act 2000* (the Act) for Dealings involving the Intentional Release (DIR) of genetically modified organisms (GMOs) into the Australian environment.

2. The Act and the Gene Technology Regulations 2001 (the Regulations), together with corresponding State and Territory legislation, comprise Australia's national regulatory system for gene technology. Its objective is to protect the health and safety of people, and to protect the environment, by identifying risks posed by or as a result of gene technology, and by managing those risks through regulating certain dealings with GMOs.

3. Section 50 of the Act requires that the Gene Technology Regulator (the Regulator) must prepare a Risk Assessment and Risk Management Plan (RARMP) in response to an application for release of GMOs into the Australian environment. Sections 50, 50A and 51 of the Act and sections 9 and 10 of the Regulations outline the matters which the Regulator must take into account and who must be consulted when preparing the RARMP.

4. The *Risk Analysis Framework* (OGTR, 2013) explains the Regulator's approach to the preparation of RARMPs in accordance with the Act and the Regulations. The Regulator has also developed operational policies and guidelines that are relevant to DIR licences. These documents are available from the Office of the Gene Technology Regulator (OGTR) website.

5. **Figure 1** shows the information that is considered, within the regulatory framework, in establishing the risk assessment context. This information is specific for each application. Potential risks to the health and safety of people or the environment posed by the proposed release are assessed within this context. **Figure 1** provides the specific information for establishing the risk assessment context for this application.

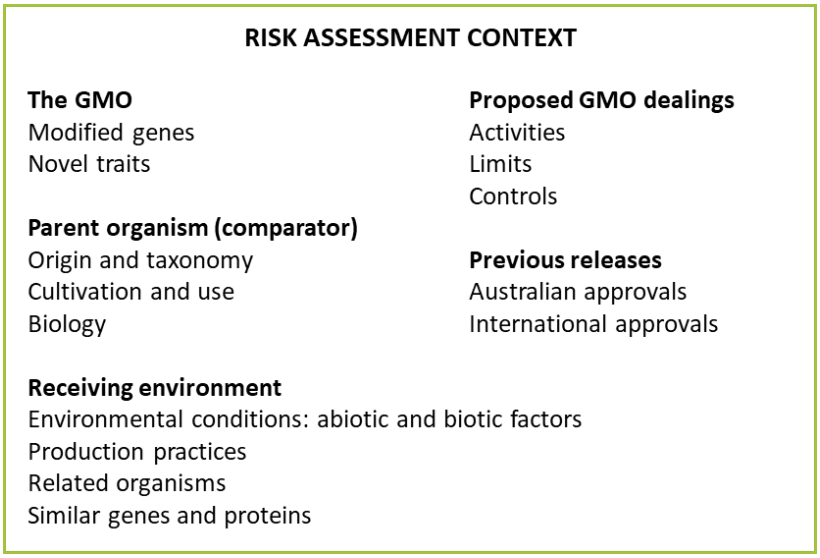

Figure 1. Summary of parameters used to establish the risk assessment context, within the legislative requirements, operational policies and guidelines of the OGTR and the RAF.

6. In accordance with Section 50A of the Act, this application is considered to be a limited and controlled release application, as the Regulator was satisfied that it meets the criteria prescribed by the Act. Therefore, the Regulator was not required to consult with prescribed experts, agencies and authorities before preparation of the RARMP.

1.1 Interface with other regulatory schemes

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

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

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

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

11. The National Health and Medical Research Council (NHMRC) has issued the *National Statement on Ethical Conduct in Human Research, 2023* (National Health and Medical Research Council et al., 2023) which is the principal ethics guideline setting out the requirements for the ethical design, review and conduct of human research in Australia. The *Therapeutic Goods Act 1989* requires an HREC to review and monitor all clinical trials of unregistered therapeutic goods. The HREC must be registered with the NHMRC and constituted and operating in accordance with the National Statement.

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

13. The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – Guideline for Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects (ICH, 2016). The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States of America, as well as those of Australia, Canada, the Nordic countries and the World Health Organization. The TGA has adopted the Integrated addendum to ICH E6(R1): Guideline for good clinical practice E6(R2) (Therapeutic Goods Administration), which provides overarching guidance for conducting clinical trials in Australia which fall under TGA regulation.

14. Some dealings with the GMO will be conducted at clinical trial sites, which are medical facilities including out-patient settings, hospitals and associated pharmacies. Analysis of biological samples

collected from trial participants administered with the GMO may occur at clinical trial sites or at pathology laboratories.

15. The State and Territory governments regulate hospitals and other medical facilities in Australia. All public and private hospitals and day procedure services need to be accredited to the National Safety and Quality Health Service (NSQHS) Standards developed by the Australian Commission on Safety and Quality in Healthcare (the Commission) and endorsed by the State and Territory Health Ministers. The Commission coordinates accreditation processes via the Australian Health Service Safety and Quality Accreditation scheme. The NSQHS Standards provide a quality assurance mechanism that tests whether relevant systems are in place to ensure that the minimum standards of safety and quality are met. The safety aspects addressed by the NSQHS Standards include the safe use of sharps, disinfection, sterilisation and appropriate handling of potentially infectious substances. Additionally, the Commission has developed the National Model Clinical Guidance Framework, which is based on, and builds on NSQHS Standards to ensure that clinical governance systems are implemented effectively and to support better care for patients and consumers.

16. The National Pathology Accreditation Advisory Council (NPAAC) advises Commonwealth, State and Territory Health Ministers on matters relating to the accreditation of pathology laboratories. NPAAC plays a key role in ensuring the quality of Australian pathology services and is responsible for the development and maintenance of standards and guidelines for pathology practices. The standards include safety precautions to protect the safety of workers from exposure to infectious microorganisms in pathology laboratories. While compliance with NPAAC standards and guidelines is not mandatory, there is a strong motivation for pathology services to comply, as Medicare benefits are only payable for pathology services if conducted in an appropriate Accredited Pathology Laboratory category, by an Approved Pathology Practitioner employed by an Approved Pathology Authority. Accreditation of pathology services is overseen by Services Australia (formerly Department of Human Services), and currently, the only endorsed assessing body for pathology accreditation is the National Association of Testing Authorities.

17. Hospitals and pathology laboratories, including their workers, managers and executives, all have a role in making the workplace safe and managing the risks associated with handling potentially infectious substances including the proposed GMO. There are minimum infection prevention practices that apply to all health care in any setting where health care is provided. These prevention practices were initially developed by the Centers for Disease Control and Prevention, and are known as the standard precautions for working with potentially infectious material. The standard precautions are described in the Australian Guidelines for the Prevention and Control of Infection in Healthcare (2024).

Section 2 The proposed dealings

18. Novotech has proposed Phase 1 clinical trial of a live GM VACV that preferentially replicates in cancer cells. The purpose of the clinical trial is to assess the safety and efficacy of the GM treatment in patients with solid tumours.

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

(a) import the GMO;

(b) conduct the following experiments with the GMO:

i. prepare the GMO for administration to trial participants;

ii. administer the GMO to clinical trial participants by intravenous (i.v.) infusion;

iii. collect samples from trial participants;

iv. analyse the samples;

(c) transport the GMO; and

(d) dispose of the GMO;

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

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

20. The clinical trial is proposed to take place over a five-year period from the date of issue of the licence. Up to 40 patients in Australia would receive a single dose of the GMO via i.v. infusion.

21. The trial would take place at hospitals and clinical sites in Australia, these sites have not yet been identified.

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

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

- Only trained personnel would conduct dealings with the GMO. Staff preparing and administering the GMO would also be experienced in the use and disposal of sharps.
- Staff considered to be at high-risk (see paragraph 32) would be excluded from handling the GMO.
- Staff preparing/administering the GMO would be required to wear appropriate PPE (e.g. gown, gloves, and eye protection) during the procedures, and instructed on how to remove and/or dispose of PPE to avoid contamination and wash the hands after PPE removal.
- Transport, storage and disposal of the GMO and any contaminated waste generated at a clinical trial site must be in accordance with the current version of the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*.
- Disinfecting surfaces and equipment that come into contact with the GMO using an effective disinfectant (including but not limited to 70% ethanol, 50% isopropyl alcohol, and/or 10% bleach).

23. The applicant has proposed several measures to limit the GMO exposure of close contacts and animals to the GMO. These include:

- The participants would be instructed to clean any household areas that may have been exposed to the GMO, including contaminated clothing, and bedding with a 10% bleach solution.
- Ensuring the administration site is kept clean and dry to prevent infection. Use of sterile, occlusive dressings to cover any pustules that develop. Changing dressings regularly and disposing of used dressings in biohazard waste bags.
- Trial participants will be instructed to avoid touching or scratching the infusion site to prevent autoinoculation and spread of the virus. Pustule kits and biohazard supplies will be provided to clinical trial participants in case of development of any pustules during the trial period.
- Instructing clinical trial participants to monitor themselves for any signs of infection or adverse reactions, such as fever, increased redness, or pus at the infusion site. Report any concerning symptoms or adverse events to a healthcare provider and the study investigator immediately.
- Participants will be instructed to avoid contact with animals and high-risk groups such as pregnant women, infants, immunocompromised individuals, and those with eczema or atopic dermatitis.

2.3 Details of the proposed dealings

2.3.1 Manufacture of the GMO

24. The GM VACV would be manufactured overseas in accordance with applicable Good Manufacturing Practice (GMP) regulations and imported into Australia (see Section 2.3.5).

Clinical trial sites

25. The clinical trial would be carried out at clinical trial sites and hospitals, which are yet to be confirmed. Clinical trial sites would be assessed by the applicant for their ability to adhere to infection prevention practices outlined in the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* (2019) (National Health and Medical Research Council, 2019). Sites would also be selected on an ability to comply with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines (ICH Guideline for Good Clinical Practice).

2.3.2 The clinical trial

26. The international sponsor for the trial is ViroMissile Inc which is headquartered in California (CA), United States of America (USA). Novotech, as a clinical research organisation (CRO), is applying for authorisation to conduct the proposed clinical trial in Australia. If the licence is approved, Novotech would be responsible for ensuring that the licence conditions are met.

27. The GM VACV would be extracted from the vial using a needle attached to a syringe and diluted in a sterile buffer solution. Once at the desired dilution, the GMO would be transferred using needle and syringe to an infusion bag. The GMO would be administered via i.v. infusion over 60 minutes and the infusion line would then be flushed with sterile saline.

28. The infusion site would be covered with an occlusive dressing until complete wound healing. The dressing should be changed daily. Contaminated dressings would be placed in a biohazard waste container (provided to the patient) and returned to the clinical trial site at the next scheduled site visit.

2.3.3 Dose levels

29. This is a Phase 1, first-in-human (FIH), open-label, dose-escalation and single arm study to determine the Maximum-Tolerated Dose (MTD) or Maximum Feasible Dose (MFD) and assess the Dose Limiting Toxicities (DLT) of the GMO. The safety and tolerability of the investigational product will be assessed in adult participants with advanced or refractory solid tumours. The total number of participants in the study will depend on the number of dose-escalation cohorts with a maximum of 40 trial participants enrolled in Australia. The applicant has stated that they may amend the protocol to include combination cohorts and expansion cohorts which may also include additional treatments. The treatment arm will follow an escalation scheme. Participants will be treated at increasing doses of study drug until all dose levels have been investigated or any dose level is found to exceed the MTD. If the DLT or the MTD are not reached, the MFD will be defined as the highest dose level.

2.3.4 Selection of trial participants and behavioural requirements

30. Relevant inclusion criteria to this assessment proposed by the applicant include that trial participants must:

- be ≥18 years-of-age at the time of signature of the informed consent form (ICF).
- women of childbearing potential (WOCBP) must have a negative serum pregnancy test prior to study entry.
- refrain from gamete donation from the first dose of the GMO, throughout the study, and for 3 months from the last dose of the GMO.
- male or female participants: Male participants with female partners of childbearing potential and female participants of childbearing potential are required to use two forms of acceptable contraception, including one barrier method, during their participation in the study and for 3 months following the last dose of the GMO.
- be willing and able to comply with all study procedures, requirements, and follow-up examinations.

31. Relevant exclusion criteria include participants who:

- are experiencing any active infections (bacterial, viral, or fungal) for which systemic antimicrobials are required.
- have known HIV infection history.
- have clinically significant immunodeficiency (e.g., due to underlying illness and/or medication) in themselves or their household contacts.
- have open wounds with current or history of severe skin disease.
- are taking certain medications (details of which are CCI and available in the CCI attachment to this RARMP).

32. For the purposes of this RARMP, persons who are pregnant or have immunosuppressive disorders are considered persons at a higher-risk of a serious adverse event when exposed to the GM VACV.

2.3.5 Transport and storage of the GMO

33. The GMO would be imported according to the packaging and labelling requirements of the International Air Transport Association (IATA) code UN 3373.

34. Transport of the GMO from the Australian border would be directly to the clinical sites or storage facility. Once at a clinical site or storage facility, the GMO would be stored in a freezer, with access restricted to appropriately trained personnel. The GMO will be contained within a sealed, unbreakable primary container and also be contained within a sealed unbreakable secondary container. The external surface of the primary and secondary container will be decontaminated before and after transport.

35. Procedures will be in place to ensure that all transported GMOs can be accounted for, and that a loss of GMOs during transport can be detected; and access to the GMOs will be restricted to authorised persons conducting dealings under the licence, who have been informed by the licence holder of any licence conditions that apply to them. This includes situations where containers are left for collection in a holding area.

36. The proposed method of supply and storage of the GMOs, as advised by the applicant, would be in accordance with the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* (TSD).

2.3.6 Sample collection and processing

37. Biological samples such as blood, urine and anal swabs will be collected for efficacy and shedding analysis on days 1,2, 3, 4, 14 and 28.

38. Blood samples will be collected by clinical site staff wearing appropriate PPE. Staff must ensure that the sample collection area is clean and sterile.

39. Urine and anal swab samples will be self-collected by trial participants within clinical settings during follow-up visits. Appropriate instruction and training will be given to trial participants before the sample collection.

40. After sample collection, clinical site staff may need to process the samples according to the study protocol. This may involve centrifugation to separate blood components, aliquoting of samples into smaller volumes for storage or analysis, or immediate processing of tissue samples for analysis. All sample processing steps will be performed following appropriate safety precautions and in compliance with Good Clinical Laboratory Practices (GCLP) or other relevant guidelines.

41. Whilst some samples such as whole blood will be analysed at site of collection, most will be shipped to a central laboratory.

2.3.7 Personal protective equipment and exclusion criteria

42. The applicant advised that persons handling the GMO, including preparation and administration of the GMO to trial participants and clean-up of potential spills, would be instructed to wear appropriate PPE, including gown, gloves, mask and eye protection.

43. The applicant has proposed that those who are pregnant or immunosuppressed would be excluded from handling the GMO.

2.3.8 Decontamination and disposal of the GMOs (including waste contaminated with the GMOs)

44. The applicant states that all GMO-contaminated waste will be handled as per the clinical waste streams of the hospital or clinic being used. This includes specific and designated containers for the disposal of biohazardous materials, including used dressings. Biohazard bags or containers will be appropriately labelled, and securely sealed to prevent leakage or accidental exposure to the virus. The bag or container would then be disposed of according to institutional or regulatory guidelines for biohazardous waste disposal, which may involve incineration or other approved methods for destruction. GMO-contaminated waste generated outside of the clinical setting, such as bandages, dressings and other materials used to care for vaccinia related lesions, would also be disposed of in biohazard bins provided to patients. The biohazard bins would be returned to the clinical trial site for disposal. In all cases, the applicant commits to follow the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*.

45. Unused GMO(s) at clinical trial sites, storage/distribution facilities and/or analytical facilities will be destroyed onsite, transported for disposal by external service providers or returned to ViroMissile. Decontamination at the trial site would be either by chemical treatment (e.g., using chemical disinfectants to treat work areas and reusable equipment) or by autoclaving. GMO spills would be decontaminated using a fresh dilution of 10% bleach, with at least 10 minutes of contact time.

2.3.9 Training of clinical trial personnel

46. If the licence is issued, Novotech would have responsibility for ensuring training of personnel and compliance with OGTR licence conditions.

47. The applicant has advised that appropriate training materials (e.g. training in all procedures specific to the GMO including preparing, handling, administration, spill procedures, containment and disposal, etc.) will be provided to all the personnel involved in the study.

48. The study drug infusion will be prepared by trained pharmacists or pharmacy technicians in a Class II Biosafety cabinet (BSC-2). Those staff would be trained on the preparation of the GMO and handling of sharps to minimise the likelihood of exposure. Additionally, at least two trained clinical trial staff need be present when the GMO administration is performed.

2.3.10 Contingency plans

49. In case of exposure of people to the GMO via sharps injury or contact with broken skin, the applicant proposes that persons who have had accidental direct contact with the GMO would be instructed to:

- bleed from the affected site; and
- scrub contaminated skin for several minutes with a 10% povidone solution (Betadine) and copious amounts of water.

50. In case of exposure of people to the GMO via aerosols, airborne droplets or direct contact with facial mucosa, the persons who have had accidental direct contact with the GMO will be instructed to rinse the affected area for a minimum of 15 minutes in eye wash or flushed with water.

51. The exposed person(s) will be monitored closely. The incident would be reported to the Principal Investigator, who would report to Novotech as soon as is practical. Novotech would then notify the Regulator.

52. In case of unintentional release of the GMO due to an accidental spill, the spill would be reported to Novotech by clinical trial staff trained in the OGTR reporting requirements. Novotech would on-report to the OGTR. The local Institutional Biosafety Committee (IBC) would also be notified of loss of containment or suspected loss of containment.

2.3.11 Accountability and monitoring

53. The applicant has proposed to instruct clinical trial participants to monitor themselves for any signs of infection or adverse reactions, such as fever, increased redness, or pus at the infusion site and report any concerning symptoms or adverse events to a healthcare provider and the study investigator immediately.

54. Any unintended exposure to the GMO through injury or direct contact would be reported to the OGTR.

Section 3 Parent organism – *Vaccinia virus*

55. The parent organism is *Vaccinia* virus (VACV). The specific strain of VACV being used by the applicant has been declared as Confidential Commercial Information (CCI), and it is discussed in a CCI attachment to this RARMP available to the prescribed experts and agencies that are consulted on the RARMP. The characteristics of the non-GM parent organism provide a baseline for comparing the potential for harm from dealings with GMOs. As such, the relevant biological properties of VACV will be discussed here.

56. VACV was used globally as a vaccine against smallpox prior to the latter's declared eradication in 1980. It was a highly effective vaccine because it is a mild pathogen that stimulates an immune response to the closely related and often lethal smallpox agent *Variola virus* (Middaugh et al., 2016). The biology of VACV has been described in detail in the RARMPs for DIR 116 and DIR 140 (clinical trials with GM VACV) and more recently in RARMPs for DIR 170 (trial with GM VACV in horses) and DIR-179 (trial with GM VACV for treatment of tumours). A summary is presented in this section.

3.1 Classification and genome characteristics

57. VACV is an enveloped virus belonging to the *Orthopoxvirus* (OPV) genus, subfamily *Chlordopxvirinae,* family *Poxviridae.* This genus also includes the human pathogen *Variola virus* (causative agent of smallpox), cowpox virus, horsepox virus, mpox virus, mousepox virus and others (McLysaght et al.; Tulman et al., 2006). *Vaccinia* virus has a roughly 195 kilobases (kb) long double stranded DNA genome which is extremely AT rich (~66%) (Li et al., 2006) and replicates in membrane bound segments localised entirely in the cytoplasm. These segments encode for the production of close to 200 proteins which facilitate viral entry, transcription of viral genes, DNA synthesis, assembly of virus particles, and suppression of the host anti-viral response (Liu et al., 2014).

3.2 Origin, geographic distribution and host range

58. Originally thought to be cowpox virus, the primary agent of smallpox vaccines was discovered to be VACV in 1939 (Downie, 1939). VACV is more closely related to horsepox and likely arose from the recombination and selection of several related *Orthopox* viruses which had been randomly combined and sampled in the pursuit of potent vaccines against smallpox (Esparza et al., 2017; Qin et al., 2015).

59. Due to their evolution in different parts of the world over nearly two centuries of smallpox vaccination, many strains of VACV exist (e.g. Paris, Copenhagen, Bern, Ankara, Lister and New York City Board of Health (NYCBH) strains). These differ in viral characteristics, host range, pathogenicity and prevalence of adverse reactions following vaccination (see Paragraph 84). Specific information about the historic use of VACV based vaccines in Australia, as well as more modern examples of use in the U.S military are discussed in the RARMP for DIR-179.

60. The host specificity of pox viruses varies widely, some such as VACV, can infect multiple hosts, whilst others such as VARV are reliant on one (Oliveira et al., 2017b; Qin et al., 2015). The natural host of VACV is not known, but in the environment and in laboratories, VACV is able to infect and cause disease in humans, several monkey species, a variety of rodents and marsupials, buffalo, dairy cattle, sheep, horses, domestic cats and dogs (Abrahão et al., 2010; Adams et al., 2007; Artois et al., 1990; Bennett et al., 1989; Brochier et al., 1989; Dumbell and Richardson, 1993; Felipetto Cargnelutti et al.,

2012; Miranda et al., 2017; Oliveira et al., 2015; Riyesh et al., 2014; Robinson and Mercer, 1988). Birds are not known to be a host for VACV, but a study of a GM VACV-based rabies vaccine demonstrated sufficient viral replication in several Canadian bird species to permit seroconversion (Artois et al., 1990).

61. Naturally occurring infections with VACV or close relatives have been documented in South America, India, Indonesia, Egypt and other countries. In Brazil, outbreaks of zoonotic disease (transferable between animals and people) caused by VACV-like viruses and affecting dairy cattle and rural workers as well as significant levels of VACV infection found in remote Amazonian wildlife have also been reported (Abrahão et al., 2010; José da Silva Domingos et al., 2021; Miranda et al., 2017; Oliveira et al., 2014).

62. There are few poxviruses in circulation in Australia, of which, mpox and *Molluscum contagiosum* are likely the only candidates with community transmission in humans since it has been several decades since the discontinuation of the smallpox vaccination campaign (Hammerschlag et al., 2022; Konya and Thompson, 1999). Mpox was first identified in Australia in 2022 and has been circulating within the community since then (Healthdirect Australia, 2024). *Molluscum contagiosum* is more prevalent but is a mild condition which predominantly affects young children or those who are immuno-compromised (Healthdirect Australia 2024).

3.3 Infection cycle

63. VACV infection is usually transmitted through physical contact with an infected lesion or pustule (Lane and Fulginiti, 2003; Wertheimer et al., 2012). Once inside the host, infectious VACV particles fuse to host cells through a process which involves at least 16 different proteins (Laliberte et al., 2011). This level of complexity is an oddity among enveloped viruses, with most requiring only one or two proteins for entry. In addition to cell fusion, VACV can also enter host cells through macropincytosis, a form of endocytosis, or via uptake from an intracellular vesicle (Mercer et al., 2010).

64. Once inside the cell, VACV disassembles, and its core navigates the microtubule network to deposit itself in a perinuclear position within the cytoplasm (Schmidt et al., 2013). Its entire replication cycle occurs in the cytoplasm, rendering the virus incapable of integrating into the host genome (Liu et al., 2014). As an additional consequence of being spatially restricted from the nucleus, VACVs are unable to use host replication enzymes and their genomes encode enzymes for DNA replication and gene transcription (Greseth and Traktman, 2022; Schramm and Locker, 2005).

65. VACV genes are expressed in three phases, early, intermediate and late (Yang et al., 2011). The mRNAs for the early phase genes are largely required for DNA replication and are expressed shortly after the virus enters the cell (Baldick and Moss, 1993). Expression of intermediate and late genes occurs post-DNA replication and needs *de novo* RNA and protein synthesis (Shors et al., 1999). These genes spur a complicated assembly and maturation process. This involves fabrication of membranes with material sourced from the host ER (Maruri-Avidal et al., 2013). These membrane bound particles will then expand, incorporating a number of viral proteins and becoming a viral replication factory (Greseth and Traktman, 2022). Once the genome has been replicated, the virions can be transported to the host cell membrane, where fusion will allow them to be released (Payne and Kristenson, 1979) (Horsington et al., 2013).

3.4 VACV persistence in infected hosts

66. There currently exists no evidence that VACV is able to persist in a latent state within an infected host. Its large genome and particle size enables efficient detection and clearance by phagocytic cells of the immune system (Buller and Palumbo, 1991). Further evidence of this is that, despite several viral variants being passaged for decades as part of global vaccination efforts, no immune evading variants of VACV have arisen.

3.5 Pathology of VACV

67. The majority of VACV variants and strains are mild pathogens in people and animals. As described in paragraph 63, the receptor binding proteins harboured by VACV are numerous. It is perhaps because of this that no single cell surface molecule has been conclusively demonstrated to be necessary for VACV virus infection. The range of cell types that VACV can infect in culture is vast but despite this, in humans, VACV primarily target antigen presenting cells and activated but not resting T cells (Chahroudi et al., 2005).

68. When contracted zoonotically, such as in the case of bovine vaccinia (BV) from milking cows or buffalos, VACV manifests as ulcerative lesions at the primary site of infection (Medeiros-Silva et al., 2010). Secondary lesions following autoinoculation have also been observed (Oliveira et al., 2017c; Tack et al., 2013). These lesions or pustules are usually accompanied by one or more of symptoms such as fever, malaise, headache, nausea and muscle aches (Medeiros-Silva et al., 2010). The lesions typically take 21 days to fully heal whilst the other general symptoms usually resolve in 3 days (José da Silva Domingos et al., 2021). When administered as a vaccine, VACV infection normally induces a single lesion at the site of exposure around 3-4 days post vaccination, which generally resolves over 2-3 weeks (Fulginiti et al., 2003a). This is often accompanied by flu-like symptoms, as described above, and swelling and tenderness of the draining lymph node (Cono et al., 2003; Public Health Agency of Canada, 2011). In healthy people, these reactions resolve spontaneously and require only observation and symptomatic treatment (Cono et al., 2003; Fulginiti et al., 2003b; Maurer et al., 2003).

69. Serious adverse reactions associated with VACV such as *post-vaccinia encephalitis* (PVE) or death are rare, strain dependent, and particularly affect those with underlying risk factors such as atopic dermatitis, or those who are immunocompromised, as in the case of AIDS (Cono et al., 2003). More information regarding severe adverse reactions specifically relating to VACV as a vaccine can be found in Section 3.10 of this Chapter.

3.6 Transmission and shedding

70. The RARMPs for DIR 140, DIR 170 and DIR-179 describe transmission (both between humans, as well as to and between animals) and shedding of VACV in detail. Importantly, transmission can occur via direct physical contact with lesions or the vaccine inoculation site or contact with a contaminated objects (e.g. bandages, clothing, sheets and towels). An infected person may also spread VACV from the initial infection site by touching other body parts or people with contaminated hands, or through every day activities such as shaving (Cono et al., 2003; Oliveira et al., 2014; Tack et al., 2013; Webber et al., 2014). Oral transmission via drinking contaminated cow milk has been observed in humans (Damaso et al., 2000). Aerosol transmission of VACV has never been clearly documented in people when used as a vaccine (Lane and Fulginiti, 2003) and is considered unlikely.

71. In the context of smallpox vaccination, VACV can be shed from the primary lesion shortly post injection and can continue for up to at least 42 days in some vaccine recipients (Pittman et al., 2015). Shedding appears to peak at between 10 and 16 days post injection and drops off dramatically in about 90% of vaccinees by day 28 (Cooney et al., 1991; Cummings et al., 2008; Wharton et al., 2003). VACV shedding has also been well demonstrated in non-human hosts, such as in the milk and faeces of experimentally infected dairy cattle, and the urine and faeces of mice, (Ferreira et al., 2008; Matos et al., 2018).

72. The minimum infectious dose of VACV is unknown. In the context of vaccination, the dose required to illicit a robust immune response to VACV varies by strain but can be achieved with as little as 2.5×10^5 pfu (Miller et al., 2008) (Jacobs et al., 2009). For those that do receive an effective dose of vaccine, their propensity to transmit active virus to close contacts is uncertain but presumed to be relatively low (Lane and Fulginiti, 2003; Neff et al., 2002; Sepkowitz, 2003; Wertheimer et al., 2012). Over 2 million vaccinations were delivered in the U.S between 2002 and 2011, and of these, only 115 cases of secondary transmission were documented (Wertheimer et al., 2012). This rate of ~5 secondary transmissions per 100,000 vaccinations almost entirely represented close physical or

intimate contacts (90%) and has been corroborated by smaller, more well controlled studies (Tack et al., 2013). It is also noteworthy that the vast majority of these infections were mild in presentation and only one life threatening event was documented. In hospital settings which contain high proportions of patients with compromised immune function and other vulnerabilities, fomite-based transmission has been observed, but not well quantified empirically (Sepkowitz, 2003).

73. In humans, viremia (viral presence in the blood) and viruria (viral presence in urine) is uncommon, although does occur in patients with progressive vaccinia and eczema vaccinatum (Lane and Fulginiti, 2003).

3.7 Recombination

74. Recombinants between Orthopoxviruses (OPVs) in cell cultures in a laboratory setting are easily produced and have been described in the RARMP for DIR 170.

75. Although replicating poxviruses can recombine very efficiently under certain circumstances, there are physical constraints within a cell that limit recombination between co-infecting viruses. VAVC transcription, translation and replication takes place in the cytoplasm but within membrane-bound cytoplasmic structures known as viral factories or virosomes (Katsafanas and Moss, 2007; Lin and Evans, 2010; Paszkowski et al., 2016), thus, compartmentalising and preventing the mixing of their nucleic acid from other viruses in the same cell (Paszkowski et al., 2016). For recombination to occur therefore, two viral factories of separate viruses in a super-infected cell would have to fuse during DNA replication.

76. For these reasons, it had long been thought that poxviruses seldom recombine naturally. However, genomic evidence suggests that recombination and horizontal gene transfer are major drivers of poxvirus evolution (Bratke and McLysaght, 2008; Brennan et al., 2023; Sprygin et al., 2022). In some instances, horizontal gene transfers appear to have conferred pox viruses with survival advantages (Bratke and McLysaght, 2008). Several poxvirus genes are thought to have been acquired and repurposed for functions such as immune evasion (Vallée et al., 2021).

77. In the case of the recent outbreak of mpox, it was demonstrated that recombination between viral isolates occurred, although the impact this had on driving the spread of the virus is unknown (Yeh et al., 2022).

78. Despite the genomic and laboratory evidence of their occurrence and possibility, concrete examples of natural poxvirus recombination are few and far between. On the whole, there still exists great uncertainty as to the frequency, mechanisms, and significance of gene flow and recombination events within poxviruses (Sprygin et al., 2022).

3.8 Environmental stability and methods of decontamination for VACV

79. Poxviruses are well known for their ability to persist in the environment, and they are more resistant to drying and increased temperature than other enveloped viruses. VACV stability is determined by temperature, relative humidity and the materials on which VACV is introduced into the environment (fomites) (Wood et al., 2013).

80. VACV survival decreases at high temperatures or high humidity and is greater at lower temperatures. Dried VACV can be kept for more than 35 weeks at 4°C with no loss of infectivity (Rheinbaben et al., 2007). When frozen (-20°C), 1 in 1000 virus particles remained viable after 15 years (Essbauer et al., 2007; Rheinbaben et al., 2007). Samples (15 mL) of VACV at $10^{7.5}$ $TCID_{50}$/mL (median Tissue Culture Infectious Dose 50%; equivalent to approximately 0.5 x 10^8 pfu) can also remain viable for more than two weeks on food samples in the fridge (4°C) or close to 6 months in storm water at 4.5°C. However, the presence of soil in stormwater decreased survival time of the VACV sample to 6 days at 4.5°C or 3 days at 21.5°C (Essbauer et al., 2007). Murine faeces exposed to environmental conditions retained infectious VACV particles for at least 20 days (Abrahão et al., 2009).

81. Purified samples of VACV are inactivated within 1 minute by a range of common chemical disinfectants including 0.5% sodium hypochlorite and 40% ethanol (Chambers et al., 2009).

82. VACV is susceptible to UV irradiation, but a small proportion (up to 10%) of virions appear to remain active when dried onto UV exposed surfaces (Sagripanti and Lytle, 2011). VACV is inactivated by dry heat at 95°C for 2 hours (Sauerbrei and Wutzler, 2009) and by autoclaving (Espy et al., 2002). Appropriate hand hygiene after contact with items that may be contaminated with VACV includes washing with antimicrobial soap and water or alcohol-based hand-rub containing 60% ethanol or more (Wharton et al., 2003).

3.9 VACV as a treatment

83. Currently, VACV is considered well-suited as a viral vector to create a new generation of safer GM vaccines and cancer treatments, such as the ones proposed within this application (Chaurasiya et al., 2020; Dyer et al., 2019; Guo et al., 2019; Harrington et al., 2019; Nagata et al., 2018). Some of the features of VACV viral vectors that make them suitable for GM cancer treatment applications are:

- thermostability, which allows for a cold-chain independent distribution capacity
- large DNA genome capable of accepting inserts of up to 25 kb
- ability to grow to high titres *in vitro*
- ability to elicit strong humoral and cell-mediated immune responses that enhance the immune response to the target antigens
- absence of oncogenic potential or evidence of integration into the host genome, and
- wide host range.

3.10 Adverse reactions to VACV infections

84. Although smallpox vaccination using VACV during the eradication campaign was generally safe and effective, serious adverse reactions have been well documented. Most complications occurred as a result of vaccination, but serious sometimes fatal, reactions occurred following transmission to unvaccinated individuals. Several types of adverse events have occurred in healthy people, while other events have been associated with specific risk factors or underlying conditions (Cono et al., 2003; Fulginiti et al., 2003b; Lane and Goldstein, 2003a; Lane and Goldstein, 2003b; Maurer et al., 2003; Neff et al., 2002; Wittek, 2006).

85. As previously mentioned, secondary transmissions are a rare occurrence. This may be in part because accidental transmission would likely generate a very limited or low infectious dose. This in turn would reduce the rate of viral progression and the proportion of cells which produce infectious virions (Howell et al., 2024).

86. Various adverse reactions may result from VACV infection including include Generalised vaccinia (GV), post-vaccinal encephalopathy (PVE), progressive vaccinia (PV), foetal vaccinia (FV), and eczema vaccinatum (EV). The most severe of these (GV, PV and PVE) are rare but can result in high levels of morbidity and even death (Kretzschmar et al., 2006; Maurer et al., 2003). FV is rare complication, with only 50 cases reported in the literature (Cono et al., 2003). It results from maternal exposure to VACV during pregnancy or shortly before conception and often leads to stillbirth or neonatal death. Due to its rarity, specific risk factors have not been determined. No other specific risks to foetuses or pregnant women have been identified. EV events are slightly more common, especially in those with a pre-existing history of eczema, but are unlikely to be fatal (Cono et al., 2003; Fulginiti et al., 2003b). Details of these adverse reactions are described in detail in DIR-179.

3.11 Treatment of adverse reactions

87. Vaccinia immunoglobulin (VIG) is made from the plasma of recently vaccinated people and has been successfully used to treat certain complications of VACV infection. It is recommended for treating severe cases of accidental implantation, severe generalised vaccinia, eczema vaccinatum and severe progressive vaccinia. It is not recommended for mild instances of accidental implantation, mild

or limited generalised vaccinia, and post-vaccinial CNS disease. VIG is contraindicated in patients with vaccinia keratitis (Centers for Disease Control and Prevention, 2020; Cono et al., 2003; Enserink, 2002; Maurer et al., 2003). In the USA, VIG has been approved as a drug for adverse reactions to the smallpox (vaccinia) vaccine. The applicant has stated that VIG will be kept in supply and made available to all involved in the trial if required.

88. Cidofovir is another drug which may be considered as a second line treatment for adverse reactions to VACV. It has a broad spectrum anti-viral activity against most DNA viruses (De Clercq, 2002). While Cidofovir has shown anti-poxviral activity *in vitro* and in mice, there is limited data on its use in humans as a treatment for vaccinia-related adverse events (Centers for Disease Control and Prevention, 2020; Maurer et al., 2003; Wittek, 2006). Cidofovir can also have severe side effects, including irreversible renal toxicity (Centers for Disease Control and Prevention, 2020; Enserink, 2002). The applicant has indicated that they would maintain a supply of Cidofovir on hand during the trial. Cidofovir is available in Australia but is not approved for the treatment of vaccinia-related complications; off-label use would thus be required.

3.12 Risk group of VACV

89. The Australian Standard 2243.3:2022 *Safety in Laboratories Part 3: Microbiological safety and containment* (Standards Australia/New Zealand, 2010, 2022) classifies VACV as a risk group 2 organism, and the Australian Immunisation Handbook recommends vaccination of people working with a repeated risk of exposure to, or working with large quantities or concentrations of, *Vaccinia virus* cultures (Australian Technical Advisory Group on Immunisation (ATAGI), 2018, 2024).

Section 4 The GMO – nature and effect of the genetic modification

90. Oncolytic viruses (OVs) are capable of replicating in cancer cells whilst having minimal impact on healthy cells. In addition to this, these viruses can be genetically modified to stimulate the hosts immune system to further recognise the cancerous cells they replicate in and subsequently mark those cells for destruction (Harrington et al., 2019). Modifications can also be made to abrogate the OVs ability to evade the host immune system and/or enhance their ability to replicate in and kill cancer cells. These properties in combination with their safety profile make OVs a promising treatment for refractory cancers (Zhang and Liu, 2020).

91. Advances in genetic-engineering and molecular virology have enabled progress in the use of OVs in cancer therapy in the last two decades. The 2015 FDA approval of the clinical use of Talimogene laherparepvec (T-VEC), a GM herpes virus for the treatment of melanoma in humans, was the first approval of its kind globally (Ferrucci et al., 2021; Johnson et al., 2015). A number of other OV treatments have demonstrated strong safety profiles in clinical studies (Chaurasiya et al., 2020).

92. Due to its desirable properties such as safety and payload capacity, multiple clinical trials utilising GM VACV as an OV backbone have already been undertaken (Guo et al., 2019). For example, a clinical trial in 16 patients with advanced solid tumours was well-tolerated in patients, resulted in selective infection in tumours, and demonstrated antitumor activity (Zeh et al., 2015). Another oncolytic VACV, known as Pexa-Vec, has had acceptable safety profiles when administered in Phase 1 and 2 clinical trials in human patients (Heo et al., 2013; Park et al., 2015). And GL-ONC1, a GM VACV based on the LIVP strain was well tolerated when administered into the peritoneal cavity of patients with advanced stage peritoneal carcinomatosis (Lauer et al., 2018).

93. The sponsor of this trial, Viromissile Inc, has developed IDOV-Immune, an oncolytic viral immunotherapy, for the treatment of patients with advanced solid tumours. IDOV-Immune is based on a vaccinia virus backbone whose derivative strain has been declared as CCI. Details of the strain used is described in the CCI attachment to this RARMP which is available to the prescribed experts and agencies that are consulted on the RARMP.

4.1 Genetic modifications to VACV

94. Viromissile Inc employed a strategy of homologous recombination (Falkner and Moss, 1990) to generate the GM VACV used in this trial. The resulting virus has 3 deleted virulence genes in addition to 3 inserted immunomodulatory genes. Disruption of these non-essential virulence genes and expression of the foreign genes not only attenuate the virus but also enhance its tumour-specific replication and boost anti-tumour immune responses.

95. The 3 inserted immunomodulatory genes are of human origin. The inserted genes activate the innate and adaptive immune response of the host to aid in eliminating the tumour cells that harbour the virus. Further information regarding the deleted and inserted genes is described in the CCI attachment to the RARMP, which is available to the prescribed experts and agencies that are consulted on the RARMP.

96. Although cancerous tumours invoke some level of innate and adaptive immune response within their microenvironment, they ultimately manage to evade critical components of the anti-tumour immune response. This immune evasion appears to be facilitated by an array of mechanisms, including the modulation of immune suppressive mediators and suppression of regulatory T-cells (Vinay et al., 2015). This observation underlies the rationale for the treatment of such tumours with an OV which can infect them and reactivate the hosts anti-tumour immune response.

97. The immune response induced by these transgenes may additionally generate a long-term immunological memory, which is capable of tumour control and prevention of recurrence.

98. There have been multiple clinical studies utilising GM VACV as an oncolytic therapy which have employed strategies incorporating deletion of virulence genes in combination with insertion of immunomodulatory genes. These studies, some of which are mentioned in paragraph 92, have largely demonstrated the safety of this approach.

4.2 Shedding and safety of the GMO

99. Viromissile Inc has conducted a number of pre-clinical studies in cell lines and a model organism aimed at determining the dynamics of viral replication, toxicity, shedding and tissue tropism of the GMO.

100. Data provided by the applicant suggests that shedding of the GMO is minimal. Biodistribution data suggest that the GMO replicates selectively in tumour cells. It should be noted that the number of animals tested is low. Also of note, is that results observed in murine models do not always translate in humans. However similar clinical trials with VACV based OVs have shown excellent safety profiles in the past. The applicant's pre-clinical results support these observations. Further details around uncertainty are presented in Chapter 2, Section 3.

101. Details of these studies have been declared as CCI and are included in the CCI attachment to the RARMP, which is available to the prescribed experts and agencies that are consulted on the RARMP.

4.3 Stability in the environment and decontamination

102. The modifications made to the VACV are not expected to have any impact on its host range, persistence in the environment, or ability to be destroyed by decontaminants.

Section 5 The receiving environment

103. The receiving environment forms part of the context for assessing risks associated with dealings with GMOs. It informs the consideration of potential exposure pathways, including the likelihood of the GMOs spreading or persisting outside the site of release.

5.1 Clinical trial sites

104. The intended primary receiving environment would be solid tumours within the clinical trial participants. As stated in Chapter 1, Section 2.3.2 each patient would receive a single dose of the GM *Vaccinia virus* as a treatment and be monitored over a period of 28 days. Administration would be via i.v. infusion.

105. The secondary receiving environment would be the hospitals and clinics where the GMO would be dispensed, administered and waste disposed of. These exact sites are yet to be identified. All clinical sites involved in the study would be equipped to handle infectious agents and procedures would be conducted in accordance with the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* (National Health and Medical Research Council, 2019).

106. The principal route by which the GM VACV as a treatment could enter the wider environment is by shedding from inoculated trial participants once they leave the hospital and return home. The tertiary receiving environment includes the trial participant's homes and any places they visit during the period when the GM VACV as a treatment is replicating and shedding.

5.2 Relevant environmental factors

107. 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.

108. The ability of the GMO to physically persist in the environment on surfaces as well as its ability to be decontaminated would be unchanged from the parent organism. These features are described in Section 3.8.

109. The parent organism, VACV, was used worldwide as a vaccine to protect against smallpox infection. The smallpox vaccination program is no longer ongoing, but the majority of people over forty years of age in Australia are likely to have been vaccinated. As a result, a proportion of the population has already been exposed to the vaccinia virus. People vaccinated may be less susceptible to VACV infection, or infection may be asymptomatic or produce less severe symptoms (Cohen, 2001; Hatakeyama et al., 2005).

110. It is widely acknowledged that people for whom smallpox vaccination is contraindicated are more prevalent in the population today than during the era of mass smallpox vaccination. For example, approximately 17% of the Australian population have a history of atopic dermatitis (Chidwick et al., 2020). There are also likely to be significant numbers taking immunosuppressive drugs for disease control (e.g. for autoimmune inflammatory conditions), organ transplant recipients and people with HIV-AIDS.

111. Animals that can be infected with the GMO may be present in environments where it could be shed by trial participants (e.g. patient's homes). Such animals are most likely to include domestic pets and, potentially, livestock.

5.3 Related viral species in the receiving environment

112. Although limited in their abundance and distribution, there are some examples of related pox viruses which exist in the Australian environment, which are discussed below.

113. *Molluscum contagiosum virus* (MCV) is one example of widely abundant, human adapted pox virus present in Australia (Konya and Thompson, 1999). Despite being a member of the poxviridae family, *Molluscum contagiosum* has no close relatives, and is the only member in its genus (Senkevich et al., 1997) The infections it causes are typically confined to children and benign. However, it is more severe and persistent in immunosuppressed patients, particularly in those with HIV/AIDS (Healthdirect Australia 2024).

114. Mpox is another member of the pox virus family present in the environment. However, the level of circulation in the Australian community has remained quite low since the outbreak in 2022 (Healthdirect Australia, 2024). Symptoms of mpox disease resemble that of other pox virus infections including fever, lymphadenopathy and pustule formation (Altindis et al., 2022). It is spread through skin to skin contact as well as contact with contaminated fomites (Alakunle et al., 2020). Although clinical presentation of mpox can be severe, it is very unlikely to result in death (Farahat et al., 2022).

115. Other more distally related and poorly characterised poxviruses are known to infect many native Australian animals, including mammals, birds and reptiles (Wildlife Health Australia, 2019). A recent example was identified in green sea turtles (Sarker et al., 2021). There have been no reports of such viruses infecting humans.

116. Similarly, the deliberately introduced myxoma virus (family Poxviridae, genus Leporipoxvirus) is not known to infect humans but is specific to rabbits and hares, causing lethal disease in some species (Águeda-Pinto et al., 2022; Kerr et al., 2022).

5.4 Presence of the introduced genes and encoded proteins in the environment

117. All 3 of the introduced genes are derived from the human genome. Therefore, humans have already been exposed to the proteins that would be produced by these genes in the GMO. However, the gene sequences have been optimised and modified for the purposes of creating the GMO.

Section 6 Relevant Australian and international approvals

6.1 Australian approvals

118. The Regulator has not previously approved any DIR or DNIR licences for dealings with the proposed GMO.

119. The Regulator has issued limited and controlled DIR licences (DIR-140 and DIR-179) utilising VACV for clinical trials in humans. The purpose of DIR-140 is to evaluate the efficacy of GM VACV for treatment of liver, kidney and prostate cancer. The Regulator has also issued a limited and controlled DIR licence (DIR-179) utilising GM VACV for the treatment of solid cancerous tumours.

6.2 International approvals

120. There are currently no other international approvals for this GMO.

Chapter 2 *Risk assessment*

Section 1 Introduction

121. 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 (The risk assessment process). Risks are identified within the established risk assessment context (Figure 2), taking into account current scientific and technical knowledge. A consideration of uncertainty, in particular knowledge gaps, occurs throughout the risk assessment process.

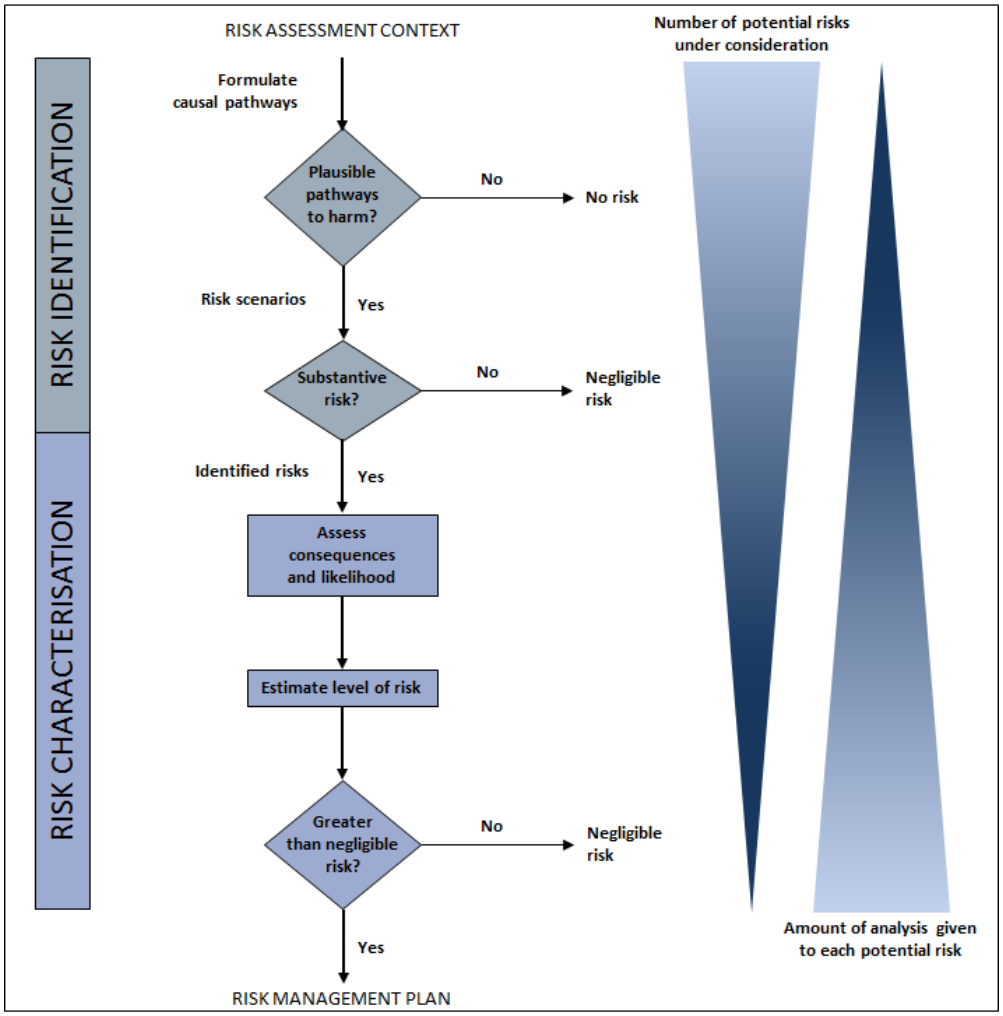

Figure 2. The risk assessment process

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

123. Risk scenarios examined in RARMPs prepared for licence applications for the same or similar GMOs, are also considered.

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

125. Risk scenarios are screened to identify substantive risks, which are risk scenarios that are considered to have some reasonable chance of causing harm. Risk scenarios that could not plausibly occur, or do not

lead to harm in the short and long term, do not advance in the risk assessment process (Figure 3), i.e. the risk is considered to be no greater than negligible.

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

Section 2 Risk identification

127. Postulated risk scenarios are comprised of three components (Figure 3):

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.

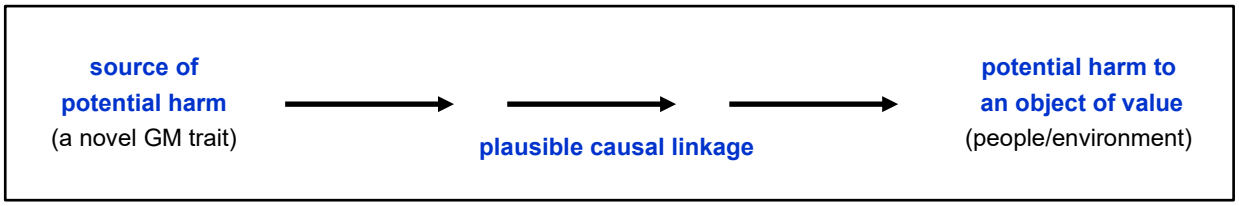

Figure 3. Components of a risk scenario

128. When postulating relevant risk scenarios, the risk context is taken into account, including the following factors detailed in Section 2:

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

2.1 Risk source

129. The parent organism of the GMO is VACV. Details on the pathogenicity and transmissibility of VACV is provided in Chapter 1 (Section 3). Vaccination with VACV tends to produce a pustule at the inoculation site. Transmission of VACV from the vaccinee to other people and susceptible hosts, such as domestic pets, could occur from this site.

130. The sources of potential harms can be intended novel GM traits associated with one or more introduced genetic elements, or unintended effects/traits arising from the use of gene technology.

131. As discussed in Chapter 1 (Section 4), the GMO has been modified by the introduction of 3 human genes and deletion of 3 viral genes, intended to produce an oncolytic trait. These modifications are considered further as sources of potential harm.

132. The expression of the introduced genes is controlled by poxviral regulatory sequences. Regulatory sequences are naturally present in all organisms and the introduced/endogenous sequences are expected to operate in similar ways to endogenous sequences. The regulatory sequences are DNA that is not expressed as a protein; they are poxvirus specific and do not present a risk in the absence of poxvirus cellular machinery. Hence, potential harms from the regulatory sequences will not be further assessed for this application.

133. The genetic modifications involving introduction of genes have the potential to cause unintended changes to viral characteristics due to insertional effects such as interruptions, deletions, duplications or rearrangements of the genome. Pathways to any unintended effects in poxviruses have been already considered in the RARMP for DIR 116, and found to be negligible. Their likelihood will be minimised by the

proposed limits and controls. These include the requirement for any unintended effects to be reported to the Regulator immediately. Therefore, the potential for the processes of genetic modification to result in unintended effects will not be considered further.

134. Infection with VACV does not result in latent infection or integration into the host genome, and this will not be considered further.

2.2 Causal pathway

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

- proposed dealings
- proposed limits including extent and scale of the proposed dealings
- proposed controls to limit the spread and persistence of the GMOs
- routes of exposure to the GMOs, the introduced gene(s) and gene product(s)
- potential effects of the introduced gene(s) and gene product(s) on the properties of the organism
- potential exposure of other organisms to the GMOs in the environment
- the environment at the site(s) of release
- spread and persistence of the GMOs (e.g. dispersal pathways and establishment potential)
- tolerance to abiotic conditions (e.g. temperature, UV irradiation and humidity)
- gene transfer by horizontal gene transfer (HGT)
- unauthorised activities, and
- practices during and after administration of the GMOs.

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

137. As discussed in Chapter 11.1 (Section 1.1), the TGA, the trial sponsor, the Investigators and HREC all have roles in ensuring the safety of trial participants under the *Therapeutic Goods Act 1989*, and human clinical trials must be conducted in accordance with the *National Statement on Ethical Conduct in Human Research* (National Health and Medical Research Council et al., 2023). Therefore, risk scenarios in the current assessment focus primarily on risks posed to people other than those participants in the trial, and to the environment.

138. *Vaccinia virus* is transmitted through direct contact. Aerosol transmission is not considered as a viable route of infection for the GMO (see Paragraph 70). Therefore, aerosol transmission will not be considered further.

139. The GMOs and samples containing the GMOs are proposed to be transported and stored in line with the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*. These are standard protocols for the handling of GMOs to minimise exposure to the GMOs, so risks associated with such transport will not be further assessed.

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

2.3 Potential harm

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

- harm to the health of people or desirable organisms, including disease in humans or animals or adverse immune response

- the potential for establishment of a novel virus in the environment.

2.4 Postulated risk scenarios

142. Three risk scenarios were postulated and screened to identify any substantive risks. These scenarios are summarised in Table 1 and examined in detail in Sections 2.4.1 - 2.4.3 (this Chapter).

143. In the context of the activities proposed by the applicant and considering both the short and long term, none of the three risk scenarios were considering to be substantive.

Table 1. Summary of risk scenarios from the proposed dealings with the GMOs

Risk scenario	Risk source	Causal Pathway	Potential harm	Substantive risk?	Reasons
1	GMO	i. Exposure of people undertaking dealings in clinical trial facilities to GMO via: ▪ needle stick/ sharps injury/ eye splash during GMO preparation, administration or sample analysis ▪ GMO contact with abraded skin ▪ contact with GMO contaminated materials ⬇ ii. Transduction of cells ⬇ iii. Replication of the GMO and expression of immunomodulatory transgenes ⬇ iv. Further transmission to people or animals	Adverse immune response Vaccinia-like disease, including serious adverse reactions	No	• Only trained and experienced personnel would prepare, administer and handle the GMO. These personnel would also be trained and experienced in the use and disposal of sharps. • Use of PPE (e.g. gown, gloves, mask and eye protection) minimises the potential for exposure to staff handling the GMO. • High-risk personnel are excluded from handling the GMO. • Sample testing would be conducted by qualified personnel in pathology or other testing laboratories. • The GMO is designed to selectively replicate in cancer cells. It is expected to be rapidly cleared by the immune response in healthy cells. • Accidental exposure would only involve a small dose of GMO and the person would receive medical attention and would be monitored for symptoms. • Exposed personnel would be instructed to cover pustules should they occur and avoid contact with high-risk groups and animals. • Inadvertent exposures with wild-type VACV in healthy people documented to date did not lead to clinically significant symptoms or did not require treatment beyond first aid and observation.
2	GMO	i. Trial participant injected/infused with the GMO ⬇ ii. The GMO is shed at the infusion sites or in body fluids	Adverse immune response Vaccinia-like disease, including serious	No	In addition to the reasons described in Risk scenario 1: • High-risk trial participants, including immunocompromised persons and pregnant people, would be excluded. • Residual inoculum GMO is unlikely to be present at the site of administration as the line would be flushed and the infusion site covered

Risk scenario	Risk source	Causal Pathway	Potential harm	Substantive risk?	Reasons
		⬇ iii. The GMO is released to the environment, exposing other people or animals to the GMO ⬇ iv. Infection of host cells ⬇ v. Replication of the GMO and expression of the immuno-modulatory transgenes ⬇ vi. Further transmission to people or animals	adverse reactions		with an occlusive dressing. The dressing would be changed every few days and disposed of in a biohazard bin. • The site of administration will be monitored for infection by participants. • Trial participants would be educated on the proper handling of wound dressings as well as towels and clothing which might come into contact with the site of administration. • All trial participants would be using barrier contraception to prevent pregnancy and transmission for at least 60 days after the last GMO treatment. • If the trial participant develops vaccinia-related lesions or pustules, they would be instructed to launder sheets and clothing separately to other laundry in soapy water. • Participants will have access to a pustule kit to appropriately clean and cover the lesions. • Bandages, dressings and other materials used to care for vaccinia-related lesions would be disposed in a biohazard bin. The biohazard bin would be returned to the clinical trial site for disposal. • The limited number of clinical trial participants and education on transmission pathways is likely to reduce potential transmission. • If exposure occurred, it is likely to be at a low dose and unlikely result in infection. The transmission rate from people who have received a VACV vaccine to other people in more recent vaccination programmes is low, as described in paragraph 72.
3	GMO	i. Trial participant injected/infused with the GMO ⬇ ii. Trial participant becomes or is already infected with another compatible virus ⬇ iii. The GMO recombines with	Novel disease in humans Establishment of novel virus with unknown pathogenicity in the environment	No	• Prior treatment with a poxvirus-based treatment or vaccine is an exclusion criteria. This reduces the likelihood of similar genomic sequences that are available for recombination. • Patients with evidence of any active systemic infection will also be excluded from the trial. • There is no reservoir of VACV in the Australian environment and limited opportunity for the GMO to come

Risk scenario	Risk source	Causal Pathway	Potential harm	Substantive risk?	Reasons
		another virus in the host ⬇ iv. Produces a replication competent recombinant virus ⬇ v. Recombinant virus is shed ⬇ vi. Recombinant virus infects new hosts and is more virulent or pathogenic.			into contact with other related poxviruses. • For recombination to occur, the GMO and another poxvirus need to be present in the same cell at the same time. • Recombination is also limited by the size of VACV and viral factory compartmentalisation. The large 25 kb deleted region, housing multiple *Vaccinia* genes would need to be acquired for the GMOs to regain its replicative ability in healthy cells.

2.4.1 Risk scenario 1

Risk source	GMO
Causal pathway	i. Exposure of people undertaking dealings in clinical trial facilities to GMO via: ▪ needle stick/ sharps injury/ eye splash during GMO preparation, administration or sample analysis ▪ GMO contact with abraded skin ▪ contact with GMO contaminated materials ⬇ ii. Transduction of cells ⬇ iii. Expression of immunomodulatory transgenes ⬇ iv. Further transmission to people or animals
Potential harm	Adverse immune response Vaccinia-like disease, including serious adverse reactions

Risk source

144. The source of potential harm for this postulated risk scenario is the GMO as a treatment.

Causal Pathway

145. There are a number of ways that people may be exposed to the GMOs while undertaking the dealings as part of this trial. The GMO treatment would be prepared and infused into clinical trial patients with solid tumours. Biological samples, including blood, anal swabs, and urine would be collected throughout the trial. During these dealings, there is a potential risk of exposure to people involved in the trial via needle stick, sharps injury and/or eye splash.

146. Exposure via needle stick may occur during the dilution of the GMO in which a syringe and needle is required to extract the GMO from the vial. It might also occur whilst administering the GMO into the i.v

bag. An eye splash might occur if either a vial containing the GMO or the i.v infusion bag used for administration is perforated or dropped.

147. Controls proposed by the applicant, including appropriate training and the use of containment equipment, would minimise this risk. Use of PPE (e.g. gown, gloves, mask and eye protection) would minimise the potential for exposure of staff handling the GMO. Sample testing would be conducted by qualified personnel in pathology or other testing laboratories, which are required to adhere to national standards for handling of infectious substances. Additionally, appropriate decontamination and disposal practices would prevent persistence and spread of the GMO.

148. In the event of an exposure, personnel would receive immediate medical attention by trained staff. The exposed individuals would then be monitored for any developing symptoms. The staff would be instructed to cover pustules should they occur and to avoid contact with high-risk groups and animals. This measure would minimise the potential transmission of the GMO to other people and animals.

149. The applicant has stated that treatments for VACV infection such as VIG will be kept on hand during dealings with the GMO.

150. The above-mentioned limits and controls would minimise the potential exposure of people to the GMOs via needle stick, sharps injury and/or eye splash.

Exposure via contact of abraded skin with infusion site

151. As mentioned in Chapter 1, Section 3.6, VACV is transmitted through close physical contact between infected and non-infected people or animals. If people in clinical trial facilities come in contact with the infusion site after patient treatment, they could be exposed to the GMO.

152. Transmission of VACV from the treated trial participant to another person would require close contact with abraded skin. The applicant has stated that the i.v. line would be flushed with sterile normal saline after administration and that the infusion site would be coved by an occlusive dressing. Together, these measures would limit the dissemination of the GMO from the infusion site.

Exposure by contact with contaminated materials

153. If people in clinical trial facilities come in contact with GMO contaminated materials, they could be exposed to the GMO. As discussed in Chapter 1, Section 3.8, VACV can remain viable for extended periods under certain circumstances. The applicant has stated that GMO waste and materials contaminated with the GMO would be disposed according to infectious medical waste management procedures (Chapter 1, Section 2.3.8). This would minimise any potential exposure to the GMO via contaminated waste.

Potential harm

154. If people undertaking dealings in clinical trial facilities are exposed to the GMOs via needle stick, sharps injury, eye splash or via close contact to an unhealed infusion site, or via GMO waste they could suffer symptoms of VACV infection, and on rare occasions an adverse immune response such as those described in Section 3.1.

155. Although the vaccinia strain modified to create the GMOs is capable of replicating in human cells, and cause illness in humans (Chapter 1, Section 3), the GMO has been modified to be selectively replication competent in cancer cells (Chapter 1, Section 4). It is expected to be cleared by the immune system if it transduces healthy cells. The three genes introduced into the GMO all stimulate the host immune response, whilst the three deleted genes limit replicative function in healthy cells. The combination of these changes increases the ability of the host to clear the virus in healthy cells. Thus, any exposure of people undertaking dealings in clinical trial facilities is unlikely to result in viral infection/disease, and depending on the level of exposure, would likely only result in an acute reaction. Inadvertent exposures with wild-type VACV in healthy people documented to date did not lead to clinically significant symptoms or require treatment beyond first aid and observation (Cono et al., 2003; Fulginiti et al., 2003b; Maurer et al., 2003).

156. Those who are immunocompromised, who are more likely to suffer a severe adverse reaction upon exposure, would be excluded from preparing or administering the GMO.

157. Although the persistent over-expression of all three immunoregulatory proteins could result in an adverse reaction, the rapid clearance of the virus would greatly reduce the risk of this occurring. Further mitigation of this risk comes in the form of the 3 deleted genes in the GMO, all of which would aid the host in clearing the virus from healthy tissues. Furthermore, the transgenes expressed by the GMO are all of human origin and therefore unlikely to be allergenic to exposed persons.

158. In addition to the points raised above, the applicant has provided some pre-clinical data which suggests that the rate of shedding of the GMO is minimal in a model organism. It also appears to replicate selectively in tumour cells. This data and its interpretation is in a CCI Attachment to the RARMP, which is available to the prescribed experts and agencies that are consulted on the RARMP.

Conclusion

159. Risk scenario 1 is not identified as a substantive risk because potential exposure would be limited by the proposed limits and controls, and the GMO is designed to selectively replicate in cancer cells. Any infection caused by the GMO is likely to be cleared by the host immune response without significant complication. Therefore, the potential for an unintentional exposure of people undertaking dealings at clinical trial sites to the GMO resulting in ill health in humans and animals is not identified as a risk that could be greater than negligible and does not warrant further detailed assessment.

2.4.2 Risk scenario 2

Risk source	GMO
Causal pathway	i. Trial participant injected/infused with the GMO ⬇ ii. The GMO is shed at the infusion site or in body fluids ⬇ iii. The GMO is released to the environment, exposing other people or animals to the GMO. ⬇ iv. Infection of host cells ⬇ v. Replication of the GMO and expression of the immuno-modulatory transgenes ⬇ i. Further transmission to people or animals
Potential harm	Adverse immune response Vaccinia-like disease, including serious adverse reactions

Risk source

160. The source of potential harm for this postulated risk scenario is the GMO as a treatment.

Causal Pathway

161. Following administration, the GMO could be shed from the patients at infusion site or in bodily fluids. It could subsequently be transmitted to a person who came into close contact with either the patient, or a patient-generated fomite.

162. The clinical trial would involve i.v. infusion as the mode of administration, leading to the presence of the GMO in the blood in the hours following administration. However, the GMO is expected to be quickly cleared by the immune system due to the modifications to the GMO, which stimulate the immune response and limit viral replication outside of cancer cells.

163. Transmissible VACV of both high and low pathogenic strains can shed into the faeces and urine of experimentally infected mice. When VACV is administered as a vaccine, viremia (viral presence in the blood) and viruria (viral presence in urine) in humans is uncommon. It does occur in patients with progressive vaccinia and eczema vaccinatum (Lane and Fulginiti, 2003). These conditions are most likely to be manifested in persons who are immunocompromised and have a history of severe skin disease, respectively. Such persons are excluded from participating in the clinical trial.

164. The applicant has proposed that all trial participants would be using barrier contraception to prevent pregnancy and transmission. This would prevent incidental transmission and pregnancy.

165. The applicant has provided some pre-clinical data which suggests that the rate of shedding of the GMO is minimal in a model organism. It also appears to replicate selectively in tumour cells. This data is discussed in the CCI Attachment to the RARMP, which is available to the prescribed experts and agencies that are consulted on the RARMP.

166. The GMO could be transmitted from the trial participants should they develop vaccinia-related skin or oral pustules. Trial participants would be informed about risks associated with the GMO and instructed to follow appropriate hygiene protocols and disposal of contaminated dressings.

167. In addition, all trial participants will be provided with a pustule management kit and those who develop lesions would be instructed to follow the pustule management plan as described in paragraph 23. The management plan would be explained to prospective participants during initial screening and anyone unwilling or unable to comply would not be enrolled in the trial. Trial participants would also be expected to seal contaminated disposable items in a provided primary container (e.g. biohazard bag) and then place this into a provided secondary container (biohazard bin). At each visit, trial participants would return the biohazard bin to the clinical trial site for disposal as clinical waste. Participants would also be advised to launder contaminated fabrics in hot soapy water. The trial participant would also be instructed to change the dressing privately, unless they require assistance from a caregiver, and limit access to any pets (particularly dogs), other animals, or higher-risk individuals (see paragraph 32). If another person or animal develops a suspicious rash, this would be reported and may be examined by the clinical trial investigator. Together, these measures would minimise potential transmission of the GMO to other people and animals.

168. The secondary transmission rate from people who have received a VACV as part of vaccination programmes is low, as described in paragraph 72. Further indication of the relatively low risk of viral dissemination is evident in a 2006 study testing a range of environmental samples that could have been in contact with a bandaged pustule from VACV infected persons. These samples were found to be negative for live virus as determined by plaque infectivity assay (Stark et al., 2006). The limited number of clinical trial participants and education on transmission pathways is likely to reduce transmission.

Potential harm

169. If people or animals (pets, wildlife, livestock) are exposed to the GMO, a range of outcomes are possible. The potential harm to people exposed to the GMO are adverse immune responses and vaccinia-like diseases and reactions as described in Risk scenario 1. If a susceptible animal is exposed to the GMO, it could lead to infection, shedding of the GMO in the environment via faeces or urine and exposure of other animals and people. This form of exposure is unlikely to cause harm because in addition to involving a low number of viral particles, the GMO was designed to preferentially replicate in cancer cells and it is expected to be cleared by the immune system if it infects healthy cells.

Conclusion

170. Risk scenario 2 is not identified as a substantive risk because potential exposure would be limited by the proposed limits and controls (including bandaging of pustules), and the GMO are designed to selectively replicate in cancer cells. Therefore, this risk could not be greater than negligible and does not warrant further detailed assessment.

2.4.3 Risk scenario 3

Risk source	GMO
Causal pathway	i. Trial participant injected/infused with the GMO ⬇ ii. Trial participant becomes or is already infected with another virus ⬇ iii. The GMO recombines with another virus in the host ⬇ iv. Produces a replication competent recombinant virus ⬇ v. Recombinant virus shed ⬇ vi. Recombinant virus infects new hosts and is more virulent or pathogenic.
Potential harm	Novel disease in humans or animals Establishment of novel virus with unknown pathogenicity in the environment

Risk source

171. The source of potential harm for this postulated risk scenario is the GMO as a treatment.

Causal Pathway

172. Should the trial participant be infected by other viruses (either incidentally or through vaccination or treatment), recombination can occur between viral types if they simultaneously infect the same cell. Similarly, another host could become infected with the GMOs through accidental exposure, and either have an existing viral infection or acquire one while the GMO is present. If recombination occurs, the introduced genes could potentially restore the replication competence of the GMO in healthy cells. The resulting novel recombinant virus could then be more readily shed from its host.

173. Even though poxviruses can infect a wide range of organisms, specific viruses have a variable host range, and some are restricted to a single host (Oliveira et al., 2017a). While recombination between different classes of virus can occur, the GM virus is more likely to recombine with another poxvirus than with an unrelated virus (see RARMP for DIR 116).

174. As described in the RARMPs for DIR 140, DIR 170, and DIR-179, *Molluscum contagiosum* virus (MCV) is likely to be present in the Australian population and MCV infection is more prevalent in school-aged children, adolescents, and young adults than in older adults (Konya and Thompson, 1999). As described in the RARMP for DIR 140, there are no reports on the ability of MCV to recombine with other poxviruses, MCV has co-existed with variola virus (the causative agent for smallpox) for thousands of years, and with VACV for over 150 years, without evidence of recombinants forming and persisting in the human population. These observations provide strong evidence that the propensity for VACV recombination with related viruses in the environment is very low.

175. In the case of mpox, whilst it is known to recombine with variants within its own strain (Yeh et al., 2022), there are no reports of mpox recombining with other pox viruses. During the first 3 quarters of 2024, approximately 700 cases of mpox have been detected Australia (Australian Government Department of Health, 2024). The symptomatic nature of most mpox infections and the fact that it is a notifiable disease, is likely to limit the degree of undetected transmission (Altindis et al., 2022; Ježek et al., 1987).

176. Although present in the Australian environment, myxoma virus only infects rabbits and hares, and is therefore unlikely to come into contact with a trial participant.

177. Although there have been reports of VACV reservoirs in Latin America (José da Silva Domingos et al., 2021), there currently exists no evidence that this has entered the Australian environment. Thus, recombination between GM and wild-type VACV because of the proposed clinical trial is highly unlikely.

178. As discussed in Risk scenario 1, the GMO is designed to be selectively replication competent and is expected to localise to cancer cells and be cleared by the immune system in healthy cells. This reduces the likelihood that co-infection of the same cells with another pox virus would occur and constitutes a barrier for potential recombination.

179. Finally, in order for a recombination event to occur with mpox, MCV or another similar poxvirus, both viruses would have to co-infect the same cells of the same person. Once this event occurred, the two viral replication factories would have to be involved in DNA replication at the same time and would have to fuse (Katsafanas and Moss, 2007; Lin and Evans, 2010; Paszkowski et al., 2016). Once the two viral replication factories had fused, compatible regions of each genome would have to be exchanged (Paszkowski et al., 2016). For this highly unlikely series of events to lead to harm, the swapped regions of the genome would have to confer increased virulence or pathogenicity. Given that the widespread use of VACV vaccines across multiple centuries has never resulted in an outcome such as the one described, the likelihood of this occurring during this trial is considered highly unlikely.

Potential harm

180. If the GMO recombines with another poxvirus, it could lead to a novel replication competent virus, it could then be shed from the host and cause disease in humans or animals, or lead to the establishment of a novel virus in the environment.

181. Any virus formed in this way, would result in progeny having any permutation of genomic segments of the two parent strains. Even in the unlikely scenario that recombination with a co-infecting poxvirus was able to generate a new replication competent poxvirus, it is not expected that recombination would lead to a virus that is more pathogenic or virulent than the wild type circulating poxvirus. This is because the deleted regions of the GMO are designed to reduce pathogenicity and the inserted genes are designed to enhance the immune response, which would likely result in enhanced viral clearance.

Conclusion

182. Risk scenario 3 is not identified as a substantive risk because recombination is unlikely due to the natural barriers to recombination, and the lack of history of recombination in poxviruses leading to harm. Therefore, this risk could not be greater than negligible and does not warrant further detailed assessment.

Section 3 Uncertainty

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

184. 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.

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

186. For DIR-208, uncertainty is noted in relation to:

- the selective replication of the GMO in cancer cells over healthy cells
- shedding of the GMO in humans

- the effect of the transgenes *in vivo*.

187. As this is a first in human trial, ViroMissile Inc has conducted several non-clinical studies in a model species. These data are provided in a CCI Attachment to the RARMP, which is available to the prescribed experts and agencies that are consulted on the RARMP. Given that the applicant's pre-clinical viral shedding studies were conducted in a model organism, it is possible that the results observed would not be replicated in human. There is uncertainty as to whether data gathered in the model species would be transferrable to humans.

188. While some uncertainty remains, it is unlikely that the GMOs would behave very differently compared to the similar stains of VACV, which have been used in humans during the smallpox eradication programme. The exact parental strain of VACV being used in this trial has not been tested before in humans and so there is a small degree of uncertainty regarding its behaviour following infection. That being said, the deletion of vaccinia genes and introduction of genes, which enhance the immune response (Chapter 1, Section 4), are designed to increase the safety profile of the GMO should it be inadvertently exposed to people other than trial participants.

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

190. Additional data, including information to address these uncertainties, may be required to assess possible future applications with reduced limits and controls, such as a larger scale trial or the commercial release of these GMOs.

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

Section 4 Risk evaluation

192. 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.

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

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

194. Three 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 1 and include:

- the GMO has been designed to selectively replicate in cancer cells
- limited ability and opportunity for the GMOs to transfer the introduced genes through recombination
- suitability of limits and controls proposed by the applicant.

195. Therefore, risks to the health and safety of people, or the environment, from the proposed release of the GMO 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[2].

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

Chapter 3 *Risk management plan*

Section 1 Background

196. 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.

197. 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 can be managed in a way that protects the health and safety of people and the environment.

198. 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 must also be reported to the Regulator.

199. 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

200. 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 trial of GMO. These risk scenarios were considered in the context of the scale of the proposed clinical trial (Chapter 1, Section 2.1), the proposed controls (Chapter 1, Section 2.2), and the receiving environment (Chapter 1, Section 5), 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

201. 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, draft licence conditions have been imposed to limit the number of trial participants, the types of sites where the GMO can be prepared and administered and the duration of the trial, as well as a range of controls 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 draft licence.

3.1 Limits and controls on the clinical trial

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

3.1.1 Consideration of limits and controls proposed by Novotech

203. The proposed clinical trial would involve a maximum of 40 participants within Australia, and most dealings with the GMOs would take place in medical facilities such as clinical trial units, hospitals and analytical laboratory facilities. Activities that would occur outside of medical facilities include transport, storage and disposal of the GMOs. The applicant has proposed to complete the study within 5 years of commencement. Conditions maintaining the risk context and proposed limits of the trial, such as the maximum number of trial participants and duration of the study, have been included in the draft licence.

204. The applicant advised that import and transport of the GMO and waste containing the GMO would be in accordance with IATA shipping classification UN 3373 [Category B] and/or the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*. These are standard protocols for the handling and minimising exposure to the GMOs. Once at the clinical trial site, access to the GMO would be restricted to appropriately trained personnel. These proposed transport conditions are suitable for the GMO. Therefore, the draft licence details the minimum requirements for packaging and labelling the GMO and waste contaminated with the GMO for transport and storage within a clinical trial site, as well as transport of the GMO for export. These measures would limit the exposure of people and the environment to the GMOs.

205. There is an ongoing multi-country outbreak of monkeypox virus and local transmission of the virus has been reported. Therefore, as a precaution, the licence requires the licence holder to provide a written methodology to reliably detect the GMO, or the presence of the genetic modifications described in this licence in a person. The written methodology must be provided to the Regulator at least 14 days prior to first administering the GMO.

206. There are proposed inclusion and exclusion criteria for both trial participants and staff as listed in Chapter 1, Section 2.3.4 and paragraph 43. The inclusion and exclusion criteria for trial participants would be subject to approval by a HREC, who would consider the safety of the individuals involved in the trial. There is limited data regarding exposure of pregnant women, young children and immunocompromised individuals to VACV. While some studies suggest that VACV vaccination does not increase the overall risk of negative pregnancy outcomes (Badell et al., 2015), the CDC advises that VACV vaccines should not be administered to pregnant women in the absence of smallpox exposure (Center for Disease Control and Prevention, 2024). Additionally, severe adverse events are strain dependent and more common in immunocompromised individuals, children under 12 months of age and those with skin disease; such groups are also excluded from VACV vaccination. Therefore, as a precaution, the draft licence requires that trial participants who are immunocompromised, suffer from severe skin disease, and women who are pregnant or breastfeeding are excluded. This also serves to minimise the potential for spread and persistence of the GMO as people in these groups are more likely to experience a serious adverse reaction. For example, the pathophysiology of skin conditions such as atopic dermatitis can result in a defective skin barrier function, epidermal hyperplasia, and abnormal immune responses, this can enable systemic spread of poxvirus infection (Reed et al., 2012). When VACV is used to vaccinate against smallpox, potential pustule formation is likely to occur within seven days. Given this, the draft licence conditions would exclude clinical trial staff who are suffering significant skin disease or immunocompromised from providing direct care for at least seven days after each infusion treatment or if pustules are present.

207. Staff who are immunocompromised and/or suffer from severe skin disease are also excluded from conducting dealings with the GMOs. In addition, as it is a first in human clinical trial, a condition is included in the licence that the licence holder should inform persons preparing and administering the GMOs of the risks associated with the GMO.

208. The applicant advised that the GMO would be administered to trial participants via i.v. infusion by clinical staff at clinical trial sites. The applicant has also proposed that clinical staff would wear PPE including gown, gloves and eye protection. These practices would minimise exposure of people handling and administering the GMOs (Risk scenario 1) and have been included in the draft licence conditions.

209. The applicant proposed to prepare the GMO in a BSC and that staff preparing and administering the GMO wear face masks. As discussed in paragraph 70 and paragraph 138, aerosols are not considered as a plausible pathway for exposure to the GMO. Therefore, the use of a BSC and face masks have not been included in the draft licence conditions.

210. Conditions are included in the draft licence requiring the licence holder to ensure that all GMOs, including material or waste that has been in contact with the GMO, within the clinical trial site, are decontaminated by autoclaving, chemical treatment or by high-temperature incineration. If external service providers are used for waste destruction this must be through a clinical waste stream.

211. The Industry Code of Practice for the Management of Clinical and Related Wastes details requirements for clinical waste including waste segregation, packaging, labelling, storage, transport and accountability (Biohazard Waste Industry, 2010). The clinical waste stream typically involves destruction of infectious waste by incineration or autoclaving, which are considered appropriate for disposal of the GMO. Given that VACV can persist in the environment (Chapter 1, Section 3.8) and compatible hosts such as rodents, marsupials and others as listed in paragraph 60 would be present in the Australian environment, disposal measures such as burial or maceration would not ensure containment. Therefore, the draft licence also requires waste disposal by external service providers to be by autoclaving or high-temperature incineration. These measures would limit the exposure of people or other animals to the GMOs.

212. The applicant has proposed to provide patients with instructions should suspicious skin pustules develop, and provide instructions to patients of good hand hygiene and cough etiquette practices. They will also provide trial participants with a pustule kit and biohazard bin, as described in paragraph 23. Together, these instructions, pustule kit and biohazard bin would limit the exposure of people or other animals to the GMOs. The applicant has also stated that the trial participant would be instructed to launder sheets and clothing in in a 10% bleach solution, and separately to other laundry, should pustule(s) develop. Given that VACV can be inactivated with antimicrobial soap and water or bleach with 0.5% sodium hypochlorite (Section 3.8), the requirement for 10% bleach has not been imposed in the draft licence conditions.

213. Part of the pustule management plan is for the trial participants to avoid high-risk individuals (paragraph 23). When VACV is used to vaccinate against smallpox, if pustule formation is to occur, it is likely to occur within seven days. Given this, licence conditions are proposed to exclude clinical trial staff for whom exclusions apply from engaging in the care of trial participants for at least seven days after each GMO administration or any time pustules are present. Children under the age of 12 months are also likely to develop serious adverse reactions should they become infected with VACV. As such, draft licence conditions include that trial participants would avoid direct physical contact with children under 12 months of age, with significant skin conditions, and persons who are pregnant or breastfeeding, for 7 days from the time of each treatment with the GMO or any time lesions are present.

214. Although there are natural barriers which limit the frequency and likelihood of poxvirus recombination, there still exists a possibility of the GMO recombining if there is co-infection in the same cell with another poxvirus. This may occur if a participant is vaccinated or treated with another poxvirus shortly before or after to the proposed trial. To limit the risk of this occurrence, a licence condition has been imposed which prevents trial participants from receiving treatment with a poxvirus-based vaccine or treatment for 30 days prior to the trial and 30 days after the last treatment with the GMO. For over 80% of VACV vaccinations, shedding is undetectable after 28 days (Pittman et al., 2015).

215. The applicant proposed that trial participants should refrain from donating blood, organs, sperm and eggs during the clinical trial and for at least 60 days after the last treatment dose. Given the health status of the trial participants, it is unlikely that they would be considered suitable donors' however, there is limited data regarding persistence, biodistribution and shedding of the GMO after treatment. Therefore, a condition has been included in the draft licence to reflect this.

216. The applicant proposed that trial participants would be instructed to use contraceptives to avoid pregnancy during the clinical trial treatment and for at least 90 days after the last treatment dose. There is limited data regarding the shedding of the GMO in body fluids. Therefore, barrier contraceptive is recommended to avoid exposure to the GMO via shedding in body fluids such as sperm and vaginal secretions, as well as to prevent pregnancy. A condition has been included in the draft licence to reflect this.

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

compliance may be achieved by only engaging persons who are required to adhere to appropriate standards to conduct the dealings.

218. Other conditions included in the draft licence are standard conditions that state that only people authorised by the licence holder are covered by the licence, and that the licence holder must inform all people dealing with the GMOs, other than external service providers, of applicable licence conditions.

219. Further conditions to be implemented in the draft licence are to ensure that a compliance management plan is in place for each clinical trial site before administration of the GMO commences at that site. The compliance management plan must detail how the licence holder intends to comply with the licence conditions, including listing persons responsible for site management, proposed reporting structures, staff training procedures and transport and disposal processes.

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

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

- limit the trial to 40 trial participants, which are to be conducted at clinical trial sites
- restrict access to the GMO
- ensure personnel involved in the trial are appropriately trained and follow appropriate behavioural requirements
- ensure appropriate PPE is used
- restrict personnel permitted to administer the GMO
- requiring decontamination of the GMO and materials and equipment that have been in contact with the GMO at clinical trial sites using effective disinfectants or disposal using a certified waste contractor in accordance with standard clinical waste disposal practices, as required by the relevant Australian and state legislation
- transport and store the GMO and samples from GMO-treated participants in accordance with IATA shipping classification UN 3373 [Category B] and/or the minimum requirements for packaging, and labelling as detailed in the draft licence.
- clinical waste stream to be used by external service providers to destroy GMO-related waste.

3.2 Other risk management considerations

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

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

3.2.1 Applicant suitability

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

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

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

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

3.2.2 Contingency plans

225. Should a licence be issued, Novotech is required to submit a contingency plan to the Regulator before commencing dealings with the GMO. This plan will detail measures to be undertaken in the event of:

- the unintended release of the GMO, including spills
- exposure of, or transmission to persons other than trial participants
- a person exposed to the GMO developing a serious adverse response.

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

226. If issued, the persons covered by the licence would be the licence holder and employees, agents or contractors of the licence holder and other persons who are, or have been, engaged or otherwise authorised by the licence holder to undertake any activity in connection with the dealings authorised by the licence. Prior to dealings with the GMO, Novotech is required to provide a list of people and organisations that are covered by the licence, or the function or position where names are not known at the time.

3.2.4 Reporting requirements

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

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

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

- identification of the clinical trial sites where administration of the GMO to trial participants would take place
- expected date of administration with the GMO for each clinical trial site
- cease of administration with the GMO for each clinical trial site.

3.2.5 Monitoring for compliance

229. 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.

230. 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.

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

Section 4 Issues to be addressed for future releases

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

- information and data that would address the uncertainties noted in Chapter 2, Section 3. Specifically, information obtained from testing for selective replication competency in cancer cells, tissue tropism and shedding of the GMOs in inoculated trial participants.

Section 5 Conclusions of the consultation RARMP

233. The risk assessment concludes that the proposed clinical trial of the GMO poses negligible risks to the health and safety of people or the environment as a result of gene technology. These negligible risks do not require specific risk treatment measures.

234. If a licence is issued, conditions are imposed to limit the trial to the proposed scale, 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.

Chapter 4 *Draft licence conditions*

Section 1 Interpretations and Definitions

1. In this licence:

   (a) unless defined otherwise, words and phrases used in this licence have the same meaning as they do in the Act and the Regulations;

   (b) words denoting a gender include any other gender;

   (c) words in the singular include the plural and words in the plural include the singular;

   (d) words denoting persons include a partnership and a body whether corporate or otherwise;

   (e) references to any statute or other legislation (whether primary or subordinate) are a reference to a statute or other legislation of the Commonwealth of Australia as amended or replaced from time to time and equivalent provisions, if any, in corresponding State law, unless the contrary intention appears;

   (f) where any word or phrase is given a defined meaning, any other part of speech or other grammatical form in respect of that word has a corresponding meaning;

   (g) specific conditions prevail over general conditions to the extent of any inconsistency.

2. In this licence:

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

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

'Clinical trial site' means a medical facility in Australia such as a clinical trial facility and associated Pharmacy, which are notified in writing to the Regulator for the purposes of conducting this clinical trial.

'Contingency Plan' means a written plan detailing measures to be taken in the event of the unintentional release of the GMOs.

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

   (a) chemical treatment;

   (b) autoclaving;

   (c) high-temperature incineration; or

   (d) a method approved in writing by the Regulator.

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

'Excluded persons' means:

   (a) persons who display any evidence of an active infection or any immunosuppressive disorder, including HIV infection;

   (b) women who are breastfeeding or who are pregnant; and women of childbearing potential (WOCBP) who are unwilling to use and document use of effective contraception for the duration of the study;

   (c) persons who have a history of significant skin disease, such as atopic dermatitis.

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

'GM' means genetically modified.

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

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

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

(a) whether the information or opinion is true or not; and

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

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

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

'Regulator' means the Gene Technology Regulator.

'Sample' means any biological material collected from an inoculated trial participant for analysis as part of the trial, and which may reasonably be expected to contain GMOs.

Section 2 'General conditions and obligations

Holder of licence

3. The licence holder is Novotech (Australia) Pty Limited.

Remaining an accredited organisation

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

Validity of licence

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

   Note: Although this licence has no expiry date, the duration of preparation and administration of the GMOs is restricted in accordance with Condition 23.

Persons covered by this licence

6. The persons covered by this licence are:

   (a) the licence holder, and any employees, agents (or External service providers engaged by the licence holder); and

   (b) the project supervisor(s); and

   (c) other persons who are, or have been, engaged or otherwise authorised by the licence holder or the project supervisor to conduct any of the dealings authorised by this licence.

7. To the extent that any activity by a trial participant may be considered to be a dealing with the GMO as described in **Attachment A** for purposes of the Act, that dealing is authorised by this licence.

8. The licence holder must keep a record of all persons covered by this licence, and must keep a record of the contact details of the project supervisor(s) for the licence.

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

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

Description of GMOs covered

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

Note: Attachment A is not included in the draft licence as the GMO is described in this Risk Assessment and Risk Management Plan.

Dealings authorised by this licence

11. The licence holder and persons covered by this licence may conduct the following dealings with the GMOs:

    (a) import the GMO;

    (b) conduct the following experiments with the GMO:

        i) prepare the GMO for administration to trial participants;

        ii) administer the GMO to trial participants by intravenous infusion;

        iii) collect Samples from trial participants;

        iv) analyse the Samples described in 11(b)iii);

    (c) transport the GMO; and

    (d) dispose of the GMO

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

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

Note: For approval to be granted, the receiving person or organisation must have an appropriate authorisation to conduct dealings with the GMOs.

Conditions imposed by the Act

Note: The Act mandates the following 3 conditions.

Informing people of licence conditions (section 63)

13. The licence holder must inform any person covered by the licence, to whom a particular condition of the licence applies, of the following:

    (a) the particular condition, including any variations of it; and

    (b) the cancellation or suspension of the licence; and

    (c) the surrender of the licence.

Note: No particular condition of this licence apply to trial participants; therefore Condition 13 does not apply to trial participants.

Monitoring and audits (section 64*)*

14. If a person is authorised by this licence to deal with the GMO and a particular condition of this licence applies to the dealing by that person, the person must allow the Regulator, or a person

authorised by the Regulator, to enter premises where the dealing is being undertaken, for the purposes of auditing or monitoring the dealing.

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

15. The licence holder must immediately inform the Regulator, if they become aware of:

    (a) additional information about any risks to the health and safety of people, or to the environment, associated with the dealings authorised by the licence; or

    (b) any contraventions of the licence by a person covered by the licence; or

    (c) any unintended effects of the dealings authorised by the licence.

Note 1: For the purposes of this condition:
(a) The licence holder is taken to have become aware of additional information if they were reckless as to whether such information existed; and
(b) The licence holder is taken to have become aware of contraventions, or unintended effects, if they were reckless as to whether such contraventions had occurred, or such unintended effects existed.

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

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

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

Informing the Regulator of any material changes of circumstance

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

    (a) any relevant conviction of the licence holder occurring after the commencement of this licence;

    (b) any revocation or suspension after the commencement of this licence, of a licence or permit held by the licence holder under a law of the Commonwealth, a State or a foreign country, being a law relating to the health and safety of people or the environment;

    (c) any event or circumstances occurring after the commencement of this licence that would affect the capacity of the licence holder to meet the conditions in it.

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

Further conditions with respect to informing persons covered by the licence

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

Note: Information required under Condition 18 may be provided to External service providers who are engaged solely for storage and transport of the GMO through labelling of the outermost container of the GMOs in accordance with Condition 38(a).

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

    (a) the licence holder has obtained from the person a signed and dated statement that the person:

i) has been informed by the licence holder of the condition and, when applicable, its variation; and

ii) has understood and agreed to be bound by the condition, or its variation; and

iii) has been trained in accordance with sub-condition 19(b) below; and

(b) the licence holder has trained that person in a manner which enables them to conduct the dealings in accordance with the conditions of this licence.

20. The licence holder must notify all persons covered by the licence, from whom Personal information relevant to the administration and/or enforcement of the licence is collected by the licence holder, that such Personal information may be disclosed to the Regulator.

21. The licence holder must ensure that a copy of the licence is readily available to all persons covered by the licence, other than External service providers, who are conducting dealings with the GMO.

Note: The licence may be made available electronically.

Section 3 Limits and control measures

Limits on clinical trials conducted under this licence

22. The GMO may be administered to a maximum of 40 trial participants.

23. The preparation and administration of the GMO must be completed within 5 years from the date of issuing of the licence.

Preparation and administration of the GMOs

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

25. The following activities must occur within a Clinical trial site:

(a) preparation of the GMO for administration to trial participants; and

(b) administration of the GMO to trial participants.

Note: Before any of these activities take place, the details of each Clinical trial site must have been notified to the Regulator in accordance with Condition 44(a).

26. The licence holder must ensure all trial participants, from the time of GMO administration, are provided with a pustule management kit, including;

(a) disposable gloves, disposable waterproof dressing, press-sealed bags, alcohol swabs, gauze; and

(b) an unbreakable secondary container appropriate for transporting waste back to the Clinical trial site. The secondary container must be labelled to indicate the contact details for the Clinical trial site; that it contains GMOs; and that it must be destroyed by autoclaving, chemical treatment or high-temperature incineration.

Note: Unbreakable means able to withstand all reasonably expected conditions of storage and transport such as: the forces, shocks and impacts expected during handling; or changes of temperature, humidity or air pressure.

Conditions relating to trial participants

27. The licence holder must notify each trial participant, from whom Personal information relevant to the administration and/or enforcement of the licence is collected by the licence holder, that such Personal information may be disclosed to the Regulator.

28. The licence holder must ensure that exclusion criteria used in selecting trial participants include (though are not limited to) the following persons:

    (a) Excluded persons as defined in this licence;

    (b) those having received live poxvirus-based treatments or vaccines 60 days prior to the first treatment with the GMO.

29. Before inoculating any trial participant with the GMO, the licence holder must obtain written agreement from the trial participant that they will:

    (a) forgo any vaccination with live poxvirus-based vaccines (as advised by licence holder), during treatment and for 60 days after last treatment with the GMO;

    (b) use barrier contraception for 60 days after each treatment with the GMO;

    (c) not donate blood, sperm, ova, tissues or organs during treatment and for 60 days after their last treatment with the GMO; and

    (d) avoid direct physical contact with children under 12 months of age and Excluded persons as defined in this licence, for at least 7 days after each treatment or any time lesions are present.

30. The licence holder must instruct the clinical trial participants in hygiene measures intended to prevent transmission of the GMO during the clinical trial. The hygiene measures must include:

    (a) thorough hand washing with soap or hand disinfectant after contact with infusion site, pustules or dressings;

    (b) cleaning household surfaces potentially exposed to the GMO with disinfectants;

    (c) washing contaminated clothing and bedding with disinfectants;

    (d) instructions on the management of the infusion site and/or pustules or skin lesions, including:

        i) preventing the exposure of other people and animals to lesions, dressings or any potentially contaminated material; and

        ii) ensuring persons caring for lesions, wear disposable gloves and wash or disinfect their hands immediately afterwards; and

        iii) sealing used dressings and other materials used in caring for the lesion in a primary container (e.g. a press-sealed bag), placing these within a secondary container (e.g. a biohazard bin) provided by the licence holder, and storing the secondary container such that it is inaccessible to children and animals until it is returned to the Clinical trial site; and

        iv) returning the secondary container referred to above, and its contents, to the Clinical trial site for disposal as clinical waste during the subsequent follow-up visit; and

        v) inform the Clinical trial site as soon as reasonably possible if they suspect that exposure such as physical contact of a lesion, to another person or to an animal may have occurred.

Conditions related to the conduct of the dealings

31. Conditions that apply to dealings with GMOs do not apply to Samples collected from trial participants, or other materials or waste, that are reasonably expected not to contain the GMO. The licence holder must provide to the Regulator upon request, a written justification for this expectation.

32. The licence holder must ensure that dealings are only conducted in a manner which:

    (a) does not compromise the health and safety of people; and

(b) minimises the exposure of persons conducting the dealings and the environment to the GMO, other than intended exposure of trial participants.

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

33. The licence holder must ensure that procedures are in place to account for the GMO from import to destruction/export, and records must be made available to the Regulator on request.

Work practices at Clinical trial sites

34. For the purposes of Condition 32 work practices and behaviours within a Clinical trial site must include, but are not limited to, the following:

(a) immunosuppressed persons or those with a history of significant skin disease must not prepare, handle or administer the GMO. In addition, these persons must not be engaged in the care of the trial participants for at least 7 days after each treatment or any time lesions are present;

(b) persons preparing and administering the GMOs must be;

i) suitably qualified and trained staff in conducting dealings with the GMOs;

ii) informed of the risks associated with the GMOs and procedures to follow in the event of exposure to the GMOs;

(c) persons preparing and administering the GMOs must wear personal protective equipment (PPE), including at least gowns, gloves, and eye protection;

(d) any broken skin (e.g. cuts, scratches, dermatitis) of persons conducting dealings not covered by PPE or clothing must be covered with a waterproof dressing;

(e) all work surfaces must be Decontaminated after they have been used for conducting dealings authorised by this licence;

(f) equipment used for dealings with the GMOs must be Decontaminated after use;

(g) the infusion site must be covered with an occlusive dressing following administration of the GMO.

Transport, storage and disposal of the GMOs

35. The licence holder must ensure that transport of the GMOs is conducted only for the purposes of, or in the course of, another dealing permitted by this licence, for supply in accordance with Condition 12, or for export.

36. For the purposes of import or export, and transport between the border and either a Storage facility or a Clinical trial site, the licence holder must ensure the GMO is packaged, labelled, stored and transported consistent with International Air Transport Association (IATA) shipping classification UN 3245/ UN 3373 [Category B].

37. Transport between a Storage facility and the clinical trial site can also be done consistent with IATA shipping classification UN/3245/3373 if the GMO is not repackaged at the Storage facility.

38. The licence holder must ensure that transport and storage of the GMO, unless conducted according to Condition 36 or 37, follows these sub-conditions:

(a) GMOs must be contained within a sealed, unbreakable primary and secondary container(s), with the outer packaging labelled to indicate at least:

i) that it contains GMOs; and

ii) that it contains biohazardous material as designated by a biohazard label; and

iii) the contact details for the licence holder; and

iv) instructions to notify the licence holder in case of loss or spill of the GMOs; and

(b) the external surface of the primary and secondary container must be Decontaminated prior to and after transport; and

(c) procedures must be in place to ensure that GMOs can be accounted for and that a loss of GMOs during transport or storage or failure of delivery can be detected; and

(d) access to the GMOs is restricted to authorised persons for whom Condition 19 or Condition 19 has been met (i.e. the GMOs are within a locked unit or an area which has restricted access). This includes situations where containers are left for collection in a holding area, or left unattended prior to Decontamination; and

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

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

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

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

(g) for the purposes of transport entirely within a building, where the GMOs are accompanied by an authorised person for whom Condition 19 has been met, Conditions 38(a)iii), 3838(a)iv) and 38(c) do not apply.

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

(a) prior to disposal, unless the method of disposal is also a method of Decontamination; and

(b) before or upon suspension, cancellation or surrender of the licence, unless covered by another authorisation under the Act, or exported; and

(c) by autoclaving, chemical treatment, high-temperature incineration or any other method approved in writing by the Regulator.

40. Where transport is conducted by External service providers for the purpose of destruction, the licence holder must ensure that the GMO, or waste reasonably expected to contain the GMO, enters the clinical waste stream for Decontamination via autoclaving or high-temperature incineration.

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

Contingency plans

41. The licence holder must ensure that any person (other than a trial participant) exposed to the GMOs is offered prompt medical treatment. The clinician must be provided with any relevant information about the GMO.

42. If there is a spill or an unintentional release of the GMOs at a Storage facility or Clinical trial site, the following measures must be implemented:

(a) the GMOs must be contained to prevent further dispersal; and

(b) persons cleaning up the GMO must wear appropriate PPE; and

(c) the exposed area must be Decontaminated with an appropriate chemical disinfectant effective against the GMOs, such as 10% bleach or 70% ethanol; and

(d) any material used to clean up the spill or PPE worn during clean-up of the spill must be Decontaminated; and

(e) the licence holder must be notified as soon as reasonably practicable.

Section 4 Reporting and Documentation

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

43. The licence holder must notify the Regulator, in writing, of the name and address of each Storage facility before commencement of dealings at that location.

44. At least 14 days prior to first administering the GMO at each Clinical trial site, or a timeframe agreed to in writing by the Regulator, the licence holder must provide the Regulator with a Compliance Management Plan for that Clinical trial site, specifying:

(a) the name, address and description of the Clinical trial site, including any associated Pharmacies/storage areas/Analytical facilities;

(b) the role and contact details for key persons responsible for the management of the trial at the site;

(c) that the Institutional Biosafety Committee (IBC) associated with the site (if any) has been notified of the trial and have been consulted regarding site specific procedures;

(d) the proposed reporting structure for the trial at the site and how the reporting structure enables the licence holder to become aware of all reportable events including but not limited to Conditions 15, 16, 45 and 46;

(e) details of how the persons covered by the licence (for that type of dealing) will be informed of licence conditions applicable to them and how they will be trained to safely conduct the dealings;

(f) details of how compliance with Condition 30 will be achieved in relation to instructing clinical trial participants in hygiene measures intended to prevent transmission of the GMO.

(g) the person(s) or class of persons administering the GMO;

(h) where, within the site, the GMO is expected to be administered;

(i) the expected date of first administration;

(j) how compliance with Condition 32 will be achieved in relation to preparation of participant Samples for analysis subsequent to administering the GMO.

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

45. For each Clinical trial site, the licence holder must notify the Regulator, in writing, of the end of the clinical trial, no later than 30 days after:

(a) the final dose being administered; or

(b) the decision that no further participants will be treated at that site.

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

    (a) in the event of a trial participant experiencing a serious adverse event which may be related to the GMO;

    (b) in the event of a loss or spill of the GMO;

    (c) in the event of the exposure of a person other than a trial participant, or animals, to the GMO; and

    (d) if a trial participant has not followed the procedures described in the instructions provided by the licence holder.

47. At least 14 days prior to first administering the GMO, the licence holder must provide to the Regulator a written methodology to reliably detect the GMO, or the presence of the genetic modifications described in this licence in a person.

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

Attachment A

DIR No: 208

Title: Clinical trial of GM vaccinia virus for the treatment of solid tumours

Organisation Details

Postal address: Novotech (Australia) Pty Limited
Level 2, 15- 31 Pelham Street
Carlton
Victoria, 3053

Phone No: (+61 3) 9491 8560

GMO Description

GMOs covered by this licence:

Vaccinia virus genetically modified by introduction or deletion of only the genes or genetic elements listed in Table 1 below.

Parent Organisms:

Common Name: *Vaccinia virus*

Scientific Name: *Vaccinia virus*

Modified traits:

Categories: Human therapeutic

Description: The GMO, known as IDOV-Immune, is a live vaccinia virus treatment derived, modified to selectively replicate in cancerous cells and to enhance the human immune response to the target cancerous tumour cells. Modified genes are listed in Table 1.

Table 1. Nucleic acid responsible for conferring the modified traits

Genetic modifications	
Source, identity, nature of modification	**Modified trait description**
Introduced genes:	Three separate genes related to immune function of human origin, which enhance anti-tumour immune responses.
Deleted genes:	The deletion of 3 VACV genes, which improves the efficacy and safety of the GMO.

Trial participants and route of administration of the GMOs

Intravenous administration to adult humans with refractory solid tumours.

Confidential commercial information (CCI)

Details of the modifications made to the GMO were declared CCI under Section 185 of the *Gene Technology Act 2000*.

Attachment B – Summary of reporting requirements*

Prior to the commencement of the trial	Condition	Timeframe for reporting
The name and address of each Storage facility	43	Before commencement of dealings at that location
A written Compliance Management Plan for each Clinical trial site: (a) the name, address and description of the Clinical trial site, including any associated Pharmacies/storage areas/Analytical facilities; (b) the role and contact details for key persons responsible for the management of the trial at the site; (c) that the Institutional Biosafety Committee (IBC) associated with the site (if any) has been notified of the trial and have been consulted regarding site specific procedures; (d) the proposed reporting structure for the trial at the site and how the reporting structure enables the licence holder to become aware of all reportable events including but not limited to Conditions 15, 16, 45 and 46; (e) details of how the persons covered by the licence (for that type of dealing) will be informed of licence conditions applicable to them and how they will be trained to safely conduct the dealings; (f) details of how compliance with Condition 30 will be achieved in relation to instructing clinical trial participants in hygiene measures intended to prevent transmission of the GMO. the person(s) or class of persons administering the GMO; (g) where, within the site, the GMO is expected to be administered; (h) the expected date of first administration; (i) how compliance with Condition 32 will be achieved in relation to preparation of participant Samples for analysis subsequent to administering the GMO.	44	At least 14 days prior to the first administration of the GMO at each Clinical trial site, or a timeframe agreed to in writing by the Regulator
For each Clinical trial site, the licence holder must notify the Regulator, in writing, of the end of the clinical trial, no later than 30 days after: (a) the final dose being administered; or (b) the decision that no further participants will be treated at that site.	45	30 days after final dose or discontinuation of participation

The licence holder must inform the Regulator as soon as reasonably possible: (a) in the event of a trial participant experiencing a serious adverse event which may be related to the GMO; (b) in the event of a loss or spill of the GMO; (c) in the event of the exposure of a person other than a trial participant, or animals, to the GMO; and (d) if a trial participant has not followed the procedures described in the instructions provided by the licence holder.	46	Immediately
At least 14 days prior to first administering the GMO, the licence holder must provide to the Regulator a written methodology to reliably detect the GMO, or the presence of the genetic modifications described in this licence in a person.	47	14 days prior to first treatment
Upon request from the Regulator, the licence holder must provide any signed records or documentation collected under a condition of this licence, within a time period stipulated by the Regulator.	48	Upon request
Information to be provided at any time during the clinical trial	**Condition**	**Timeframe for reporting**
Any additional information related to the health and safety of people and the environment associated with the dealings covered by the licence, or any unintended effects of the dealings authorised by the licence	15(a), (c)	Immediately
Information related to any contravention of the licence by a person covered by the licence	15(b)	Immediately
Any relevant conviction of the licence holder	16(a)	Immediately
Any revocation or suspension of a licence or permit held by the licence holder under a law of the Commonwealth, a State or a foreign country	16(b)	Immediately
Any event or circumstances that would impact the licence holder capacity to meet the licence conditions	16(c)	Immediately

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