Australian Government
Department of Health, Disability and Ageing
Office of the Gene Technology Regulator

November 2026

Risk Assessment and Risk Management Plan

(Consultation Version) for

DIR 232

Clinical trial of a GM vaccinia virus (CLD-401) for the treatment of advanced solid tumours

Applicant – Avance Clinical Pty Ltd

20 November 2026

This RARMP is open for consultation until 8 January 2027.

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

Via the consultation hub: https://consultations.health.gov.au (search for DIR 232)

via email to: ogtr@health.gov.au

or

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

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

Summary of the Risk Assessment and Risk Management Plan (Consultation Version)
for
Licence Application No. DIR 232

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 Dealing involving the Intentional Release (DIR) of GMOs into the Australian environment under the *Gene Technology Act 2000*.

The applicant, Avance Clinical Pty Ltd, proposes to conduct a clinical trial to evaluate the safety, tolerability 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 a limited number of participants 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, Avance Clinical Pty Ltd would be subject to the requirements of 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. Avance Clinical Pty Ltd would also require approval from the Department of Agriculture, Fisheries and Forestry (DAFF) for import of the GMO into Australia.

The Regulator has prepared a Risk Assessment and Risk Management Plan (RARMP) for this application, which concludes that the proposed clinical trial pose negligible to moderate risks to the health and safety of people and the environment. Licence conditions have been drafted for the proposed clinical trial and risk treatment measures have been proposed to mitigate moderate risks. The Regulator invites submissions on the RARMP, including draft licence conditions, to inform the decision on whether to issue a licence.

The application

Project Title	Clinical trial of a GM vaccinia virus (CLD-401) for the treatment of advanced solid tumours
Parent organism	Vaccinia virus (VACV)
Principal purpose	The proposed trial is a Phase 1 study designed to evaluate the safety, efficacy and tolerability of a genetically modified virus, for the treatment of Australian clinical trial participants with advanced solid tumours.
Genetic modifications	Two introduced genes[1] of human origin including: • A modified interleukin-15 (IL-15) to generate an immune response • A modified cluster of differentiation 55 (CD55) to improve the efficacy of the GMO Three deleted VACV genes including: • Thymidine Kinase (TK) to improve the selectivity against cancer cells • Vaccinia Growth Factor (VGF) and A46R to increase the safety of the GMO
Previous clinical trials	This is a first in human clinical trial using this GMO
Limits and controls	
Duration	5 years
Number of participants	A limited number of clinical trial participants in Australia
Locations	The proposed trial would be conducted at hospitals and clinics across Australia. The exact clinical trial sites are yet to be identified
Controls	• provide instructions to trial participants about appropriate hygiene practices • transport and store the genetically modified organism (GMO) according to transport, storage and disposal guidelines appropriate for PC2 GMOs • require staff handling the GMO to be trained and to use personal protective equipment • exclude higher risk staff from handling the GMO • destroy waste that may contain GMO according to clinical site procedures appropriate for PC2 GMOs.

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.

[1] Some details about the inserted genes in the GM VACV have been declared as Confidential Commercial Information 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.

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 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 to moderate risks to human health and safety and to the environment. Specific risk treatment measures are required to manage these moderate risks. Important factors in reaching the conclusions of the risk assessment included that the GM VACV treatment is enriched for replication in cancer cells, and unintended exposure to the GMOs would be minimised by the limits and controls.

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.

As the level of risk is considered negligible to moderate, specific risk treatment is required. Specific risk treatment conditions intended to minimise exposure and transmission of the GMO include providing trial participants with instructions particularly around hygiene practices and potential pustule management.

As this is a clinical trial, the licence also includes limits on the number of participants, the facilities that may be used and the duration of the trial, together with a range of controls to minimise the potential for the GMO to spread in the environment. In addition, the licence contains general conditions relating to licence holder suitability, auditing, monitoring and reporting requirements, including the obligation to report any unintended effects.

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Abbreviations

°C	Degrees Celsius
CCI	Confidential Commercial Information
CDC	Centres 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
IV	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
VARV	*Variola* 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. Chapter 1 provides the specific information for establishing the risk assessment context for this application.

RISK ASSESSMENT CONTEXT

The GMO
Modified genes
Novel traits

Parent organism (comparator)
Origin and taxonomy
Cultivation and use
Biology

Proposed GMO dealings
Activities
Limits
Controls

Previous releases
Australian approvals
International approvals

Receiving environment
Environmental conditions: abiotic and biotic factors
Production practices
Related organisms
Similar genes and proteins

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

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. 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.

8. For clinical trials, the TGA has regulatory responsibility for the supply of unapproved therapeutic products. In terms of risk to individuals participating in a clinical trial, the TGA (as the primary regulatory agency), the trial sponsor, the investigators and the Human Research Ethics Committee (HREC) at each trial site all have roles in ensuring participants' safety under the *Therapeutic Goods Act 1989*. However, where the trial involves a GMO, authorisation is also required under gene technology legislation. To avoid duplication of regulatory oversight, and as risks to trial participants are addressed through the above mechanisms, the Regulator's focus is on assessing risks posed to people other than those participating in the clinical trial, and to the environment. This includes risks to people preparing and administering the GM virus, and risks associated with import, transport and disposal of the GMO.

9. The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – Guidelines for Good Clinical Practice (ICH-GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects (ICH 1996). The guideline was developed with consideration of the current good clinical practices of the European Union (EU), Japan, and the United States of America (USA), as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO). The TGA has adopted the ICH-GCP in principle as Note for Guidance on Good Clinical Practice (designated CPMP/ICH/135/95) (Therapeutic Goods Administration 2000), which provides overarching guidance for conducting clinical trials in Australia which fall under TGA regulation.

10. The National Health and Medical Research Council (NHMRC) has issued the *National Statement on Ethical Conduct in Human Research* (National Health and Medical Research Council et al., 2018). This document sets the Australian standard against which all research involving humans is reviewed. The *Therapeutic Goods Act 1989* requires that the use of a therapeutic good in a clinical trial must be in accordance with the ethical standards set out in this document.

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

12. DAFF administers Australian biosecurity conditions for the importation of biological products under the *Biosecurity Act 2015*. Biological products include animal or microbial derived products such as foods, therapeutics, laboratory materials and vaccines (including GMO).

13. Analysis of biological samples collected from trial participants administered with the GMO would occur at clinical trial sites, or at pathology laboratories. These facilities are regulated by State and Territory governments and adhere to professional standards for safety, disease control (Australian Guidelines for the Prevention and Control of Infection in Healthcare (2019) and handling of pathology samples (National Pathology Accreditation Advisory Council; NPAAC).

14. 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 (APL) category, by an Approved Pathology Practitioner (APP) employed by an Approved Pathology Authority (APA). 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 (NATA).

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 (AHSSQA) 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. 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 (CDC) 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 (2019).

Section 2 The proposed dealings

17. Avance Clinical Pty Ltd has proposed a 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, efficacy and tolerability of the GM treatment in clinical trial participants with advanced solid tumours.

18. 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 (IV) 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)*

19. The clinical trial is proposed to take place over a five-year period from the date of issue of the licence. A limited number of clinical trial participants in Australia would receive multiple doses of the GMO via IV infusion, every 28 days until confirmed tumour progression by iRECIST (Immune Response

Evaluation Criteria in Solid Tumours), a framework that standardises the assessment of tumour responses to immunotherapies (RECIST Working Group, 2026). Treatment would also cease in the event of dose-limiting toxicity, participant withdrawal, or termination of the study.

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

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

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

- 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 and/or 0.5% sodium hypochlorite (bleach)).

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

- Covering the IV administration site with an occlusive dressing and disposing of any contaminated dressings through biohazard and clinical waste stream processes.
- Maintaining strict hand hygiene following contact with the administration site, body fluids, or potentially contaminated materials.
- Avoiding the sharing of personal items that may be contaminated with body fluids and laundering potentially contaminated clothing, towels and bedding separately.
- Regularly disinfecting bathroom surfaces and ensuring any open wounds or skin lesions are appropriately covered.
- Avoiding close contact with at-risk individuals, including immunocompromised persons, pregnant women, infants, individuals with active skin conditions, and elderly persons with compromised immune function, for 28 days following treatment.
- Limiting close contact with animals, including household pets and livestock susceptible to vaccinia virus infection.
- 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 who are immunocompromised or pregnant 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) and instructed on how to remove and/or dispose of PPE to avoid contamination and wash the hands after PPE removal.
- Offering smallpox vaccination of staff conducting dealings and in close contact with clinical trial participants after GMO administration
- Using barrier contraception during sexual activity for the protocol-specified period following treatment.
- Not donating blood, plasma, organs or tissues for at least 12 weeks following administration.
- Not sharing needles or injection equipment.
- Reporting any unusual skin lesions, rashes, suspected viral infections, or illnesses in close contacts to the clinical team.

2.3 *Details of the proposed dealings*

2.3.1 Manufacture of the GMO

23. The GM VACV would be manufactured overseas in accordance with applicable Good Manufacturing Practice (GMP) regulations and imported into Australia (see Section 2.4).

2.3.2 Clinical trial sites

24. The clinical trial would be carried out at clinical trial sites and hospitals, which are yet to be determined. 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 their 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).

2.3.3 The clinical trial

25. The international sponsor for the trial is Calidi Biotherapeutics. Avance Clinical Pty Ltd is a clinical research organisation (CRO), responsible for conducting the proposed clinical trial in Australia. As the licence holder, Avance Clinical Pty Ltd is responsible for ensuring that the licence conditions are met.

26. The GM VACV would be extracted from the single use screwcap cryovial with integrated seal 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 IV infusion, and the infusion line would then be flushed with sterile saline.

27. The infusion site would be covered with an occlusive dressing until complete wound healing. The dressing would be changed by the participant or healthcare provider every 48 hours until healed. Contaminated dressings would be placed in a biohazard waste container (provided to the clinical trial participants) and returned to the clinical trial site at the next scheduled site visit.

2.3.4 Dose levels

28. This is a Phase 1, first-in-human (FIH), open-label, dose-escalation study to determine the optimal biological dose and recommended Phase 2 dose of the GMO. The safety, tolerability and efficacy of the investigational product would be assessed in adult participants with advanced solid tumours. The doses are expected to range from $1x10^8$ to $5x10^9$ PFU. Clinical trial participants would receive escalating doses every 28 days until tumour progression, dose-limiting toxicity is reached, clinical trial participant withdraws or the study is terminated.

2.3.5 Selection of trial participants

29. 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 following 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 2 months following the last dose of the GMO.

30. Relevant exclusion criteria include participants who:

- Active autoimmune diseases
- Pregnant or breast-feeding
- Have household contacts who are pregnant
- Active eczema or a history of severe eczema
- Ongoing severe inflammatory skin conditions

- active and clinically significant infections (bacterial, viral, or fungal) including known hepatitis B virus, known hepatitis C virus, known HIV or AIDS - related illness
- Concurrent participation in other clinical studies

2.4 *Transport and storage of the GMO*

31. The GMO would be imported and unused GMO exported according to the packaging and labelling requirements of the International Air Transport Association (IATA) code UN 3245.

32. Clinical trial participant samples containing the GMO would be exported according to the packaging and labelling requirements of IATA code UN 3373

33. 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 would be contained within a sealed, unbreakable primary container, which would be contained within a secondary sealed unbreakable container. The external surface of the primary and secondary container would be decontaminated before and after transport.

34. Procedures would be in place to ensure that all transported GMOs can be accounted for, and that a loss of GMOs during transport can be detected. Access to the GMOs would 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.

35. 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).

2.5 *Sample collection and processing*

36. Biological samples such as blood, urine, swabs (injection sites, the oropharynx, and anogenital area) and tumour tissue biopsies would be collected for efficacy and shedding analysis. 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.

37. Specimens would be collected by clinical site staff wearing appropriate PPE (Section 2.6). Staff must ensure that the sample collection area is clean and sterile.

38. Some samples may be processed on site while others would be transported to pathology laboratories for analysis.

2.6 *Personal protective equipment and exclusion criteria*

39. The applicant stated that persons handling the GMO, including for preparation and administration of the GMO to trial participants and for cleaning up any spills, would be instructed to wear appropriate PPE, including gown, gloves (recommended double gloving), mask and eye protection.

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

41. Smallpox vaccination would be offered to clinical trial staff conducting dealings with the GMO and/or in close contact with clinical trial participants.

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

42. The applicant states that all GMO-contaminated waste would 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 would 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 bag/containers provided to clinical trial participants. The biohazard bags/containers would be returned to the clinical trial site for disposal. In all cases, the applicant would follow the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*.

43. Unused GMO(s) at clinical trial sites, storage/distribution facilities and/or analytical facilities would be destroyed onsite, transported for disposal by external service providers or returned overseas. 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 0.5% bleach, with at least 10 minutes of contact time.

2.8 *Training of clinical trial personnel*

44. Avance Clinical Pty Ltd would be responsible for training of personnel and compliance with OGTR licence conditions.

45. The applicant stated that personnel handling and administering the GMO would receive specific training in all procedures specific to the GMO including preparing, handling, administration, sharps training, BSL-2 practices (BSL-2 is the US equivalent of PC2), spill management procedures, containment and waste disposal.

46. The study drug infusion would be prepared by trained pharmacists or pharmacy technicians in a Class II Biosafety cabinet (BSC-II).

2.9 *Contingency plans*

47. In the event of exposure of a person to the GMO via sharps injury or contact with broken skin, the applicant proposes that the affected person would be instructed to:

- allow the wound to bleed freely;
- wash the affected area thoroughly with soap and water for at least 5 minutes;
- apply an antiseptic solution (e.g. povidone-iodine or chlorhexidine); and
- cover the wound with a sterile dressing.

48. The incident would be reported and documented. The affected person would undergo a clinical assessment within 24 hours and be monitored for 21 days for signs of infection. If infection occurs, treatment with tecovirimat and/or Vaccinia Immune Globulin (VIG) may be considered.

49. In the event of exposure of a person to the GMO via aerosols, airborne droplets or inhalation, the applicant proposes that the affected person would be instructed to:

- move immediately to fresh air;
- remove any contaminated clothing; and
- rinse their mouth with water without swallowing.

50. The incident would be reported and documented. The affected person would undergo a clinical assessment and be monitored for 21 days. Post-exposure vaccination may be considered based on the outcome of the clinical assessment. Aerosol transmission of vaccinia is considered unlikely and has not been clearly documented in humans.

51. In the event of direct contact of the GMO with facial mucosa, the applicant proposes that the affected person would be instructed to:

- immediately flush the affected area thoroughly with water; and

- irrigate the eye with water for at least 15 minutes in the event of ocular exposure.

52. The incident would be reported and documented. The affected person would undergo a clinical assessment and be monitored for 21 days. Ocular exposures would require urgent ophthalmological assessment. If ocular vaccinia infection develops, treatment with topical antivirals such as trifluridine may be considered.

53. In the event of ingestion of the GMO, the applicant proposes that the affected person would be instructed to:

- rinse their mouth; and
- drink small amounts of water to dilute the material.

54. The incident would be reported and documented, including the estimated quantity ingested. The affected person would undergo a clinical assessment and be monitored for 21 days.

55. In the event of a splash of the GMO onto the skin or contamination of clothing, the applicant proposes that the affected person would be instructed to:

- immediately remove contaminated clothing; and
- wash the affected skin thoroughly with soap and water for at least 5 minutes, including showering if a large area is affected.

56. Significant exposures would be reported and documented. The affected skin would be inspected for breaks or abrasions that could permit viral entry, and the affected person would undergo a clinical assessment and be monitored for 21 days if skin integrity had been compromised.

57. In the event of an accidental spill or other unintentional release of the GMO, the incident would be reported to Avance Clinical Pty Ltd by clinical trial staff trained in OGTR reporting requirements. Avance Clinical Pty Ltd would notify the OGTR. The relevant Institutional Biosafety Committee (IBC) would also be notified of any loss, or suspected loss of containment. Personnel responsible for cleaning up GMO spills would wear appropriate PPE consistent with PC2 requirements. This would include double nitrile or latex gloves, a fluid-resistant disposable gown or coveralls, eye protection (goggles or a face shield), and dedicated or disposable footwear. For larger spills, additional protection such as an impermeable apron, boot covers, head covering and an N95 respirator would be used.

2.10 *Accountability and monitoring*

58. The applicant has proposed to monitor participants for signs of vaccina infection through clinical assessments, sample collection, adverse event reporting and evaluation of close contacts

- Participants would be instructed to report any illness in close contacts, with suspected transmission leading to clinical assessment, notification of investigators and OGTR, and confirmation using PCR.
- Confirmed transmission cases would be managed by infectious disease specialists, with supportive care for mild infections and consideration of antiviral treatments or Vaccinia Immune Globulin.
- Contact tracing, monitoring of exposed individuals, infection control measures, and, where appropriate, post-exposure vaccination would be implemented to prevent further spread.
- A 21-day monitoring period would be recommended for close contacts following the participant's administration of the GMO.
- Close contacts identified as at-risk (immunocompromised, pregnant, eczema history, infants) would be offered direct follow-up by the clinical trial team

59. All suspected and confirmed transmission would be reported including notifying OGTR. Detailed records would be maintained throughout the trial.

Section 3 Parent organism – *Vaccinia* virus

60. The parent organism is *Vaccinia* virus (VACV). The specific strain of VACV being used by the applicant has been declared as CCI. 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.

61. 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), DIR-179 and DIR-208 (trials with GM VACV for treatment of tumours). A summary is presented in this section.

3.1 *Classification and genome characteristics*

62. 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 (previously known as monkey pox) virus, mousepox virus and others (McLysaght et al.; Tulman et al., 2006). *Vaccinia* virus has a roughly 195 kilobase (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*

63. 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).

64. 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 99). 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.

65. The host specificity of pox viruses varies widely, some such as VACV, can infect multiple hosts, whilst others such as Variola virus (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).

66. 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).

67. 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, 2026) *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*

68. 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 macropinocytosis, a form of endocytosis, or via uptake from an intracellular vesicle (Mercer et al., 2010).

69. 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 for enzymes for DNA replication and gene transcription (Greseth and Traktman, 2022; Schramm and Locker, 2005).

70. 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).

71. VACV produces several distinct virion forms during its replication cycle. The two mature infectious forms are the intracellular mature virion (IMV) and the extracellular enveloped virion (EEV), with intermediate forms including the intracellular enveloped virion (IEV) and cell-associated enveloped virion (CEV) (Smith and Vanderplasschen, 1998). IMVs are formed in the cytoplasm and constitute the majority of virus particles produced during infection(Smith and Vanderplasschen, 1998). A proportion of IMVs acquire additional membrane layers to become IEVs, which are transported to the cell periphery where they fuse with the plasma membrane to form CEVs (Smith and Vanderplasschen, 1998). While CEVs remain attached to the cell surface and promote local cell-to-cell spread through actin-based motility, some are released as EEVs into the extracellular environment (Roberts and Smith, 2008). Although EEVs comprise less than 1% of total virions they are critical in the vaccinia replication cycle by enabling efficient long-range dissemination of the virus, facilitating spread to distant cells and tissues beyond the initial site of infection (Roberts and Smith, 2008).

3.4 *VACV persistence in infected hosts*

72. There is currently no evidence that VACV persists 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 *Transmission and shedding*

73. The RARMPs for DIR 140, DIR 170 , DIR-179 and DIR-208 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 object (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 when used as a vaccine has never been clearly documented in people (Lane and Fulginiti, 2003) and is considered unlikely.

74. 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).

75. 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 (Jacobs et al., 2009; Miller et al., 2008). 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 most 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).

76. Even small amounts of virus that initially replicate only at the site of infection can spread throughout the body before the adaptive immune response is activated (Davies et al., 2017). In most cases, these circulating viruses are controlled and contained by the innate immune response, preventing widespread infection (Davies et al., 2017).

77. 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).

3.6 *Recombination*

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

79. Although replicating poxviruses can recombine very efficiently under certain circumstances, there are physical constraints within a cell that limit recombination between co-infecting viruses. VACV 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.

80. 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).

81. 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).

82. Despite the genomic and laboratory evidence of their occurrence and possibility, concrete examples of natural poxvirus recombination are rare. 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).

3.7 *Environmental stability and methods of decontamination for VACV*

83. 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 it is introduced into the environment (fomites) (Wood et al., 2013).

84. 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).

85. 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).

86. 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).

3.8 *VACV as a treatment*

87. 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 one proposed within this application (Chaurasiya et al., 2020b; Dyer et al., 2019; Guo et al., 2019; Harrington et al., 2019; Nagata et al., 2018; Xu et al., 2024).

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
- Replicate exclusively in the cytoplasm, no integration of viral DNA into host genome making it safe with no identified oncogenic potential
- Wide host range
- Tumour tropism, potential for systemic administration
- Rapid and lytic replication cycle
- Replication in hypoxic conditions
- High infectivity in a range of tissues

3.8.1 Oncolytic VACV and cancer immunotherapy

88. Tumours invoke some level of innate and adaptive immune response within their microenvironment; however, they ultimately manage to evade critical components of the anti-tumour immune response. This immune evasion is facilitated by an array of mechanisms, including the modulation of immune suppressive mediators and suppression of regulatory T-cells (Vinay et al., 2015). Oncolytic viruses (OVs) can infect tumours and reactivate the hosts anti-tumour immune response.

89. OVs can replicate in cancer cells whilst having relatively minimal impact on healthy cells. 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 whilst sparing healthy cells (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 widely deployed treatment for refractory cancers (Xu et al., 2024; Zhang and Liu, 2020).

90. 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., 2020b).

91. 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). Initially oncolytic VAVCs were administered intra-tumourally. For example, a clinical trial in 16 participants with advanced solid tumours was well-tolerated, resulted in enriched replication in tumours, and demonstrated antitumour 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 participants (Heo et al., 2013; Park et al., 2015). GL-ONC1, a GM VACV based on the LIVP strain was well tolerated when administered into the peritoneal cavity of individuals with advanced stage peritoneal carcinomatosis (Lauer et al., 2018). Recently oncolytic VACVs have been developed for IV administration, as opposed to intra-tumourally. In clinical trials, intravenous oncolytic VACVs exhibit good safety and potential anti-tumour activity (Xu et al., 2024). There are no preexisting neutralizing antibodies in most human bodies, however, after oncolytic VACV treatment, neutralizing antibody generation occurred, limiting the efficacy of repeated systematic delivery (Xu et al., 2024).

92. Oncolytic VACVs destroy tumour tissues *via* three main mechanisms: direct oncolysis of tumour cells, disrupting tumour vasculature and activating anti-tumour immunity (Figure 2) (Xu et al., 2024).

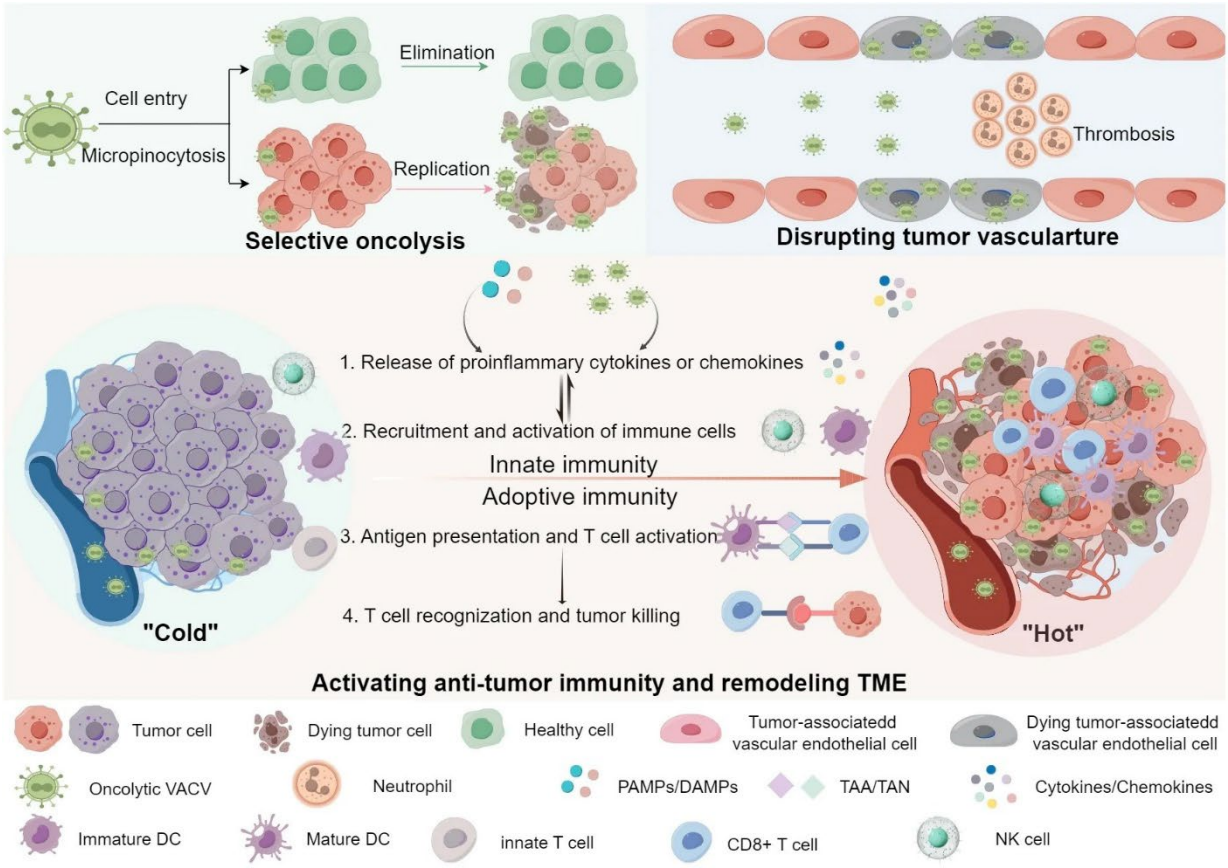


Figure 2: Anti-tumour mechanisms of oncolytic VACVs.

93. Direct tumour cell lysis: oncolytic VACVs selectively infect and replicate within tumour cells, causing cell lysis and facilitating spread to neighbouring tumour cells. Disruption of tumour vasculature: oncolytic VACVs can infect tumour-associated vascular endothelial cells, leading to vascular damage, inflammatory cell recruitment, and thrombosis within the tumour. Activation of anti-tumour immunity: Viral replication and tumour cell lysis release tumour antigens and inflammatory signals that stimulate innate and adaptive immune responses, enhance tumour-specific T-cell responses and promote immune-mediated tumour clearance. Adapted from (Xu et al., 2024)

94. The preferential lysis of tumour cells by oncolytic VACVs is due to biological differences between tumour and healthy cells. The down regulation of tumour suppressor and antiviral genes facilitates viral survival and replication in tumour cells (de Queiroz et al., 2019). Additionally, the deletion of viral genes such as Thymidine Kinase (TK) in the oncolytic VACV, limits the ability of the virus to replicate in healthy cells. This is because TK is more abundant in tissue actively dividing, such as tumour cells, allowing faster replication of the virus (Puhlmann et al., 2000a).

3.8.2 Oncolytic VACV-based immune-related combination therapies

95. The effectiveness of oncolytic VACVs is limited by host antiviral immune responses, particularly interferon (IFN) signalling, and by tumour heterogeneity (Xu et al., 2024). Genetic modifications that enable expression of immunostimulatory factors have been introduced into oncolytic VACVs to improve their therapeutic efficacy.

96. Pro-inflammatory cytokines, including interleukin (IL)-12, IL-23 and IL-15, have been engineered into GM oncolytic VACVs and have been shown to enhance anti-tumour immune responses (Shakiba et al., 2023; Xu et al., 2024). These engineered viruses can promote T-cell and natural killer (NK) cell

activation and cytotoxicity, while also increasing interferon production, thereby strengthening anti-tumour immunity.

3.9 *Adverse reactions to VACV infections*

97. VACV is generally a mild pathogen in humans and animals. VACV encodes numerous immunomodulatory proteins that interfere with host immune responses and a range of attachment and receptor-binding proteins that contribute to its broad cellular tropism (Hernaez and Alcamí, 2020). Although VACV can infect a wide variety of cell types in vitro, infection in humans primarily involves antigen-presenting cells and activated, but not resting, T cells (Chahroudi et al., 2005).

98. Human VACV infection, including zoonotic infections such as bovine vaccinia, typically presents as localised ulcerative lesions at the site of infection, with secondary lesions occasionally occurring following autoinoculation (Medeiros-Silva et al., 2010; Oliveira et al., 2017c; Tack et al., 2013). Lesions are commonly accompanied by systemic symptoms including fever, malaise, headache, nausea and myalgia (Medeiros-Silva et al., 2010). Lesions generally resolve within approximately three weeks, while systemic symptoms usually resolve within several days (José da Silva Domingos et al., 2021). Following vaccination with VACV-based vaccines, a single lesion typically develops at the inoculation site within 3-4 days and resolves over 2-3 weeks. Swelling and tenderness of regional lymph nodes and mild flu-like symptoms may also occur (Cono et al., 2003; Fulginiti et al., 2003a; Public Health Agency of Canada, 2011). In immunocompetent individuals, these reactions are generally self-limiting and require only symptomatic management (Cono et al., 2003; Fulginiti et al., 2003b; Maurer et al., 2003).

99. The VACV-based smallpox vaccination was generally safe and effective, rare but serious adverse reactions have been reported following both vaccination and secondary transmission of VACV. Adverse events include generalised vaccinia (GV), post-vaccinal encephalopathy (PVE), progressive vaccinia (PV), foetal vaccinia (FV) and eczema vaccinatum (EV) (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). GV, PV and PVE are rare but may result in severe morbidity and, in some cases, death (Kretzschmar et al., 2006; Maurer et al., 2003). FV is an uncommon complication associated with maternal exposure during pregnancy or shortly before conception and has been linked to stillbirth and neonatal death; however, only approximately 50 cases have been reported in the literature (Cono et al., 2003). EV occurs more frequently than these complications, particularly in individuals with a history of eczema, but is rarely fatal (Cono et al., 2003; Fulginiti et al., 2003b). Further details of these adverse reactions are described in detail in DIR-179.

3.9.1 Treatment of adverse reactions

100. 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-vaccinia CNS disease. VIG is contraindicated in individuals 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 would be kept in supply and made available to all involved in the trial if required.

101. 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.

3.10 *Risk group of VACV*

102. The Australian Standard 2243.3:2022 *Safety in Laboratories Part 3: Microbiological safety and containment* (Standards Australia/New Zealand, 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), 2022).

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

103. The GMO (CLD-401) is an oncolytic viral immunotherapy, for the treatment of advanced solid tumours. The GMO is based on a vaccinia virus backbone whose derivative strain has been declared as CCI. The functions of genes or genetic elements that have been modified, introduced or deleted, and the effects of the changes on phenotype of the GMO have been provided in Table 1.

4.1 *Genetic modifications to VACV*

Table 1. Genetic modifications made to generate the GMO

Genetic modifications	Promoter	Modified trait.	The effects of the changes on phenotype of the GMO
Insertion of CD55-A33R	pSL (synthetic early promoter)	Expression of chimeric A33R+CD55 fusion protein	Protects against complement-mediated neutralisation
Insertion of IL-15 Super Agonist (SA)	pSL (synthetic early promoter	Expression of IL-15 Super Agonist	Activation of NK and CD8+ T cells enhances anti-tumour immune responses.
Deletion of VGF (vaccinia growth factor)	NA	Complete loss of vaccinia viral growth factor	Viral Attenuation
Deletion of J2R (Thymidine kinase)	NA	Complete loss of vaccinia thymidine kinase activity	Improves tumour selection in vivo (Puhlmann et al., 2000b)
Deletion of A46R (hemagglutinin)	NA	Complete loss of A46 protein	Viral Attenuation

4.1.1 Inserted Transgenes

CD55-A33R

104. A33R is a VACV gene that encodes a highly conserved glycoprotein that is incorporated into the outer viral envelope (Roper et al., 1998; Wolffe et al., 2001). CD55, also known as decay-accelerating factor (DAF), is a membrane-bound complement regulatory protein that inhibits complement activation, limiting immune-mediated cell lysis (Geller and Yan, 2019). Complement inhibition by CD55 has been linked to the suppression of adaptive immune responses in vivo (Geller and Yan, 2019). The GMO expresses a CD55-A33R fusion protein under the synthetic late promoter, it is incorporated into the EEV membrane, where CD55 provides protection against complement-mediated neutralisation. This increased resistance to host immune clearance has been associated with prolonged viral survival in circulation and improved efficacy following intravenous administration (Lee et al., 2023; Xu et al., 2024). CD55 is commonly overexpressed in cancer, where it promotes tumour survival, immune evasion, treatment resistance and disease progression through protection from complement-mediated lysis and activation of oncogenic signalling pathway (Geller and Yan, 2019). As CD55 expression is restricted to the outer envelope of the VACV, any immune-evasion or other biological effects of CD55 are limited to the vaccinia virus and are not expected to result in any broader effects associated with sustained CD55 expression.

IL-15 SA

105. Interleukin-15 (IL-15) is a cytokine primarily expressed by activated monocytes, macrophages and dendritic cells, promoting the activation, proliferation, survival and cytotoxic function of natural killer (NK) cells and CD8+ T cells, including the maintenance of memory CD8+ T cell populations (Knudson et al., 2020). IL-15 signals through pathways that are closely related to those used by IL-2, a cytokine that has been extensively investigated as a cancer immunotherapy, but differs in its ability to support cytotoxic lymphocyte responses without preferentially expanding regulatory T cell populations (Knudson et al., 2020). Overexpression of IL-15 can lead to inflammation but has also been found to promote tumour destruction and reduce metastasis in breast cancer (Gillgrass et al., 2015). In preclinical cancer models, IL-15-based immunotherapies, including recombinant IL-15, IL-15/IL-15Rα superagonists, consistently demonstrated anti-tumour activity (Fiore et al., 2020). Reported outcomes include tumour regression in melanoma, delayed tumour growth in colon and epithelial carcinomas, increased NK-cell and CD8+ T-cell tumour infiltration, inhibition of lung metastases, prolonged survival of tumour-bearing animals, and complete tumour remission (Fiore et al., 2020).

106. IL-15/IL-15Rα complexes are referred to as IL-15 superagonists (SA) because they are engineered to produce more potent and sustained immune stimulation than native soluble IL-15 through enhanced receptor engagement, stability and improved pharmacokinetic properties (Han et al., 2011; Knudson et al., 2020). The antitumour activity of IL-15 SAs is driven by their ability to enhance cell-mediated immunity. IL-15 SAs have been investigated as immunotherapeutic agents designed to augment antitumour immune responses and improve the efficacy of other cancer therapies (Knudson et al., 2020; Wrangle et al., 2018; Xu et al., 2024).

107. While the specific IL-15 SA in this GMO has not been trialled in humans, FDA and EMA approved IL-15 SA, ALT-803, also known as ogapendekin alfa inbakicept, N-803 and commercially as Anktiva (Kim et al., 2016; Rhode et al., 2016). In preclinical studies, ALT-803 promoted the development of highly functional NK cells and innate phenotype CD8+ T-cell responders, increased NK-cell activity, and contributed to reduced tumour metastasis and improved survival outcomes in tumour-bearing mice (Kim et al., 2016; Rhode et al., 2016). However repeated cycles of ALT-803 injection may lead to reduced biological responsiveness in NK cells of individuals with metastatic non-small cell lung cancer (Wrangle et al., 2018).

108. Pharmacokinetic studies in mice demonstrated that ALT-803 has a circulating half-life of approximately 25 hours and that a single intravenous dose resulted in significant expansion of both

CD8+ T cells and NK cells (Han et al., 2011). There was retention of ALT-803 in lymphoid organs in mice (Rhode et al., 2016). In human clinical trials, ALT-803 has been well-tolerated, with no dose-limiting toxicity, and main adverse reactions restricted to skin rashes at injection site and resolving fevers (Peng et al., 2022).

109. While IL-15 SAs have demonstrated potent immune-stimulatory activity, their enhanced biological effects may also increase the risk of adverse immune outcomes. In mice, IL-15 SA treatment was associated with dose- and time-dependent hypothermia, weight loss, liver injury and mortality, demonstrating the potential for IL-15 SA-mediated immunotoxicity (Guo et al., 2015). More broadly, the potent activation and expansion of NK cells and T cells could potentially contribute to immune cell exhaustion, excessive production of pro-inflammatory cytokines, autoimmunity or other immune-mediated toxicities (Knudson et al., 2020). Systemic administration of high-dose IL-15 in humans is associated with significant toxicity; however, it is better tolerated when delivered locally, such as via subcutaneous injection at doses of up to 3 µg/kg (Tan and Waldmann, 2020). The applicant claims that the 3-4hr half-life of their IL-15 SA agonist will mitigate the risk of systemic cytokine mediated toxicities.

110. IL-15 may, under certain circumstances, exert pro-tumorigenic effects. IL-15 can function as a growth and survival factor for malignant cells that express the IL-15 receptor complex, including cutaneous T-cell lymphoma, T-cell large granular lymphocyte leukaemia, multiple myeloma and T-cell leukaemia cells (Fiore et al., 2020; Ma et al., 2022; Mishra et al., 2016; Zhang et al., 2008). In vitro studies have shown that IL-15 supports the proliferation of malignant lymphoid cells and inhibits apoptosis, while in vivo administration of recombinant IL-15 has been associated with enhanced tumour growth in some tumour models (Ma et al., 2022). Prolonged exposure to supraphysiological levels of IL-15 has also been linked to malignant transformation, with transgenic mouse models and human large granular lymphocytes when exposed to overexpressed IL-15 developing NK-cell, NKT-cell and T-cell leukemias and lymphomas(Ma et al., 2022; Mishra et al., 2012; Zhang et al., 2008).

111. IL-15 exhibits both tumour-promoting and anti-tumour activities in solid cancers, with its overall effect depending on tumour type, receptor expression, and the cellular context of signalling. Elevated intratumoural IL-15 levels and increased circulating sIL-15Rα or sIL-15/IL-15Rα complexes have been associated with poor clinical outcomes in head and neck cancer, lung cancer, melanoma, renal cell carcinoma, and colon cancer (Fiore et al., 2020). IL-15 can promote tumour cell proliferation, migration, invasion, angiogenesis, epithelial-mesenchymal transition, resistance to apoptosis, and immune escape (Fiore et al., 2020).

112. Prolonged or repeated exposure to elevated IL-15 or sIL-15/IL-15Rα complexes can be detrimental, as sustained stimulation has been shown to induce fatal T/NK-cell leukaemia in mice, impair NK-cell activation, proliferation and cytotoxic function, and promote NK-cell hypo-responsiveness or exhaustion (Felices et al., 2018; Fiore et al., 2020). Repeated stimulation with IL-15 in individuals with cancer may result in further detrimental outcomes. One IL-15 infusion led to an increase in NK cell expansion and proliferation, a second infusion of rhIL-15 resulted in a decrease in NK cell responses (Fiore et al., 2020).

113. While IL-15 can enhance anti-tumour immunity, sustained, uncontrolled or high concentration of IL-15 signalling may promote the growth, survival and malignant transformation of susceptible cell populations, particularly haematological malignancies expressing IL-15 receptors.

4.1.2 VACV deleted genes

J2R (Thymidine Kinase)

114. Thymidine Kinase (TK) is an enzyme which is essential to DNA replication in both eukaryotic cells and viruses as it is required to liberate thymidine triphosphate. VACV encodes its own TK named J2R, and without it, its replication is severely impinged. In recognition of this phenomenon, many OV based cancer treatments have adopted the approach of deleting TK (Chaurasiya et al., 2020a; Foloppe et al., 2019). The GMO has the J2R locus deleted, and the virus is thus TK deficient.

115. Unlike healthy eukaryotic cells which only express high levels of TK when replicating their DNA, tumour cells often exhibit constitutive expression of TK (Hengstschläger et al., 1994). This means that an otherwise attenuated TK deficient virus could still replicate in tumour cells by making use of their relatively high levels of TK. In this way, the GMO has been engineered to have enriched replication in tumour cells and less efficient replication in healthy cells.

VGF

116. The vaccinia virus growth factor (VGF) gene encodes a polypeptide with sequence homology to epidermal growth factor (EGF) and transforming growth factor-α and is present at both ends of the vaccinia virus genome within the inverted terminal repeat regions (Buller et al., 1988). VGF binds to EGF receptors in infected and neighbouring uninfected cells, stimulating cellular proliferation and supporting viral spread, as VACV replicates most efficiently in actively dividing cells (Guse et al., 2011). This function is largely dispensable in tumour tissues because cancer cells have enhanced proliferation and provide a permissive environment for viral replication (Guse et al., 2011). Deletion of the VGF gene can reduce viral replication and spread in cells with low rates of proliferation while maintaining replication within tumours and other rapidly proliferating cell populations, thereby enhancing tumour selectivity and attenuating virulence (Guse et al., 2011). Consistent with this, VGF deletion has been associated with reduced virulence and an improved safety profile while preserving oncolytic activity (Beerli et al., 2019; Buller et al., 1988; Guse et al., 2011; Xu et al., 2024).

117. In oncolytic VACVs, simultaneous deletion of J2R and VGF genes further enhances tumour selectivity by restricting efficient viral replication and spread to tumour cells and other rapidly proliferating cells such as ovarian cells (McCart et al., 2001; Xu et al., 2024). Attenuation of J2R and VGF double Knock Out (KO) VACV is seen in non-tumour cells (including bone marrow and spleen) while no attenuation and WT levels of replication are seen in tumour and ovary cells (McCart et al., 2001). This attenuation translates into increased safety by reducing the risk of progressive vaccina, no toxicity was found in nude mice at 10^8 PFU and no virus recovered from brains compared to fatalities in WT and single deletion mice (McCart et al., 2001). The double KO VACV demonstrates enhanced tumour-specific replication and reduced virulence in non-tumour cells, improving the safety profile of the virus (McCart et al., 2001; Xu et al., 2024; Zeh et al., 2015).

A46R

118. The A46R gene encodes an immunomodulatory protein (A46) that inhibits innate immune signalling pathways. A46 interferes with Toll-like receptor (TLR) and interleukin-1 (IL-1) signalling by binding to TIR-domain-containing adaptor proteins, including MyD88, TRIF, MAL and TRAM (Stack et al., 2005). A46 suppresses activation of the NF-κB, MAPK and IRF3 pathways reducing host antiviral immune responses which contributes to VACV virulence (Perdiguero et al., 2013; Stack et al., 2005).

119. The A46R KO VACV has enhanced oncolytic activity compared with WT VACV. In vitro studies showed that ΔA46R VACV exhibited superior tumour cell cytotoxicity, increased viral replication and improved viral spread in tumour cell lines (Ho et al., 2021). In vivo, viral replication following administration of A46R KO VACV localised primarily to tumours and the ovaries in mice (Ho et al., 2021). A46R KO VACV was undetectable in the ovaries of non-human primates six days following intravenous administration (Ho et al., 2021). A46R deletion was associated with increased T-cell infiltration into tumours, suggesting that loss of A46R-mediated immune suppression may also enhance anti-tumour immune responses.

120. Deletion of A46R results in VACV that has a reduced capacity to inhibit host innate antiviral mechanisms. Non-tumour cells are better able to mount antiviral defences that limit successful viral propagation, whereas tumour cells, which frequently possess defective antiviral responses, remain susceptible to infection and replication (Ho et al., 2021). A46R KO VACV shows viral attenuation in non-tumour cell lines (Perdiguero et al., 2013). The proposed GMO has the A46R locus deleted. This contributes to enhanced tumour selectivity, tumour cytotoxicity and viral attenuation in non-tumour cells.

4.2 *Biodistribution of the GMO*

121. The applicant has provided data from pre-clinical biodistribution studies in mice which suggest that the GMO replicates efficiently and preferentially in tumour cells and poorly in other cells. It should be noted that these studies were limited in nature and scope. Results observed in animal models do not always translate in humans. However, similar clinical trials with VACV based OVs have shown strong safety profiles in the past. 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*

122. 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

123. 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*

124. The intended primary receiving environment would be solid tumours within the clinical trial participants. As stated in Chapter 1, Section 2.3.3 each clinical trial participants would receive multiple doses every 28 days of the GM VACV as a treatment and be monitored over a period of 28 days. Administration would be via IV infusion.

125. The secondary receiving environment would be the hospitals and clinics where the GMO would be dispensed, administered and where GMO containing waste would be 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).

126. 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 therapeutic GM VACV is replicating and shedding.

5.2 *Relevant environmental factors*

127. 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.

128. 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 3.7 .

129. The parent organism, VACV, was used worldwide as a vaccine to protect against smallpox infection. Following the eradication of smallpox in 1980, routine vaccination programs ceased. In Australia, vaccination was not undertaken on a population-wide basis, with quarantine and border controls serving as the principal measures for preventing disease (MacIntyre et al., 2018). While some healthcare workers, defence personnel, and migrants vaccinated overseas may have been exposed to VACV, overall population exposure is expected to be limited (MacIntyre et al., 2018). A 2018 study estimated that no more than 30% of Sydney residents born before 1980 were likely to have received a smallpox vaccine (MacIntyre et al., 2018). Using Sydney as a representative or the broader national population, the majority of Australians are unlikely to have prior exposure to VACV. The few who

were vaccinated may be less susceptible to VACV infection, or infection may be asymptomatic or produce less severe symptoms (Cohen, 2001; Hatakeyama et al., 2005).

130. 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). In 2018, it was estimated that approximately 17% of Sydney's population, which may be considered broadly representative of the Australian population, was immunosuppressed (MacIntyre et al., 2018).

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

5.3 *Related viral species in the receiving environment*

132. 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.

133. *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 individuals , particularly in those with HIV-AIDS (Healthdirect Australia 2024).

134. 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, 2026; 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).

135. 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.

136. 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*

137. All of the introduced genes are derived from the human genome. Therefore, humans have already been exposed to the proteins that would be produced by 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*

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

139. The Regulator has issued limited and controlled DIR licences (DIR-140, DIR-179 and DIR-208) 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 limited and

controlled DIR licences (DIR-179 and DIR-208) utilising GM VACV for the treatment of solid cancerous tumours.

6.2 *International approvals*

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

Chapter 2 *Risk assessment*

Section 1 Introduction

141. 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 3), taking into account current scientific and technical knowledge. A consideration of uncertainty, in particular knowledge gaps, occurs throughout the risk assessment process.

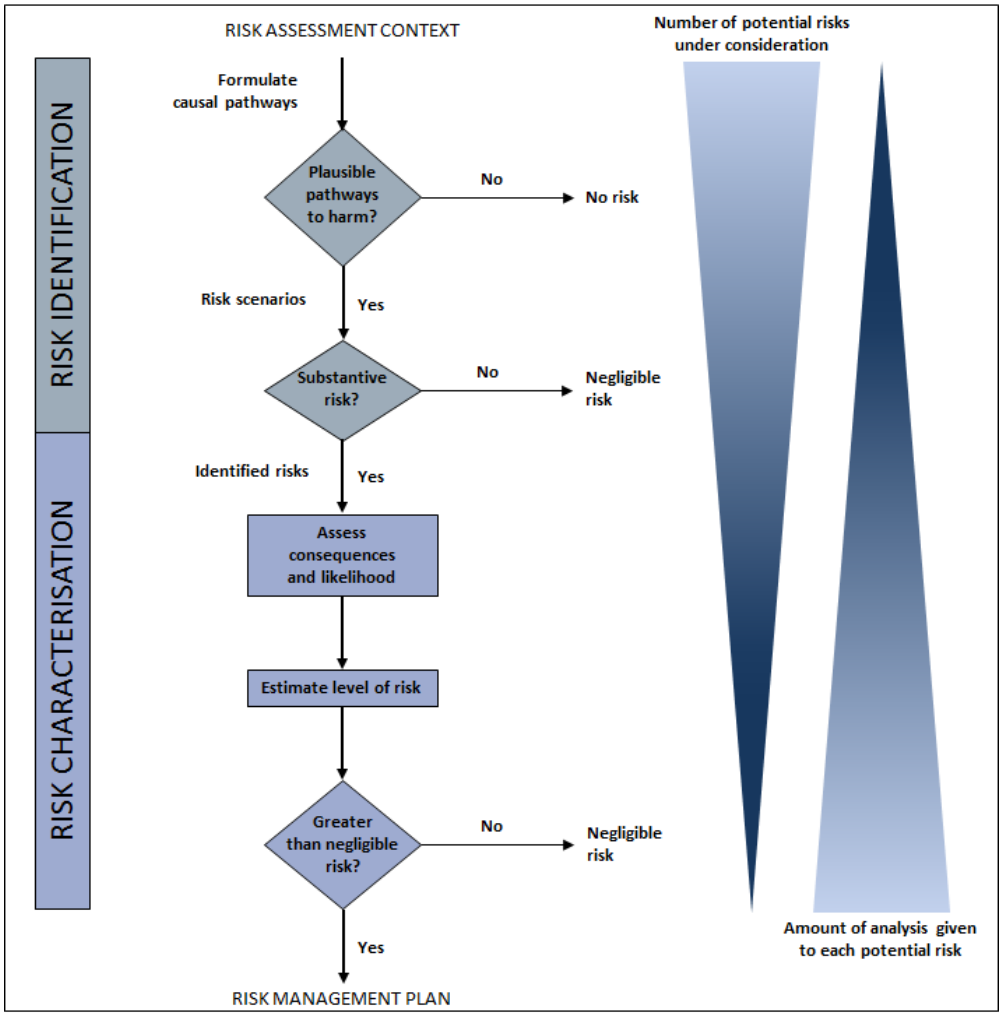


Figure 3. The risk assessment process

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

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

144. 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.

145. 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.

146. 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

147. Postulated risk scenarios are comprised of three components (Figure 4):

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.

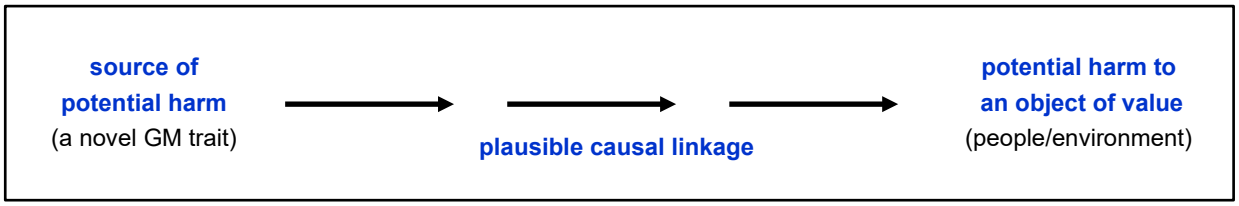


Figure 4. Components of a risk scenario

148. 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*

149. The parent organism of the GMO is VACV. Details on the pathogenicity and transmissibility of VACV are 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.

150. 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.

151. As discussed in Chapter 1 (Section 4), the GMO has been modified by the introduction of 2 human genes and deletion of 3 viral genes, intended to produce an oncolytic trait. These modifications are considered further as sources of potential harm.

152. While the inserted human gene IL-15 SA has been widely used for the treatment of cancers, there are reports of pro-tumour effects associated with its use (Section 4.1.1). In the context of oncolytic immunotherapy, expression of these proteins is intended to enhance immune activation and tumour destruction. However, dysregulated or sustained expression of IL-15 has been implicated in the development, survival and progression of certain tumour types. IL-15 overexpression can stimulate growth and survival for cancers particularly haematological malignancies and has been associated with malignant transformation under conditions of prolonged or excessive exposure. This risk will be considered further.

153. The expression of the introduced genes is controlled by synthetic 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.

154. 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.

155. 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*

156. 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.

157. Although 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.

158. As discussed in Chapter 1 (Section 0), 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.

159. *Vaccinia* virus is transmitted through direct contact. Aerosol transmission is not considered as a viable route of infection for the GMO (see Paragraph 76). Therefore, aerosol transmission will not be considered further.

160. Furthermore, all transgenes expressed by the GMO are derived from human proteins and are therefore unlikely to be allergenic to exposed persons. The potential for the GMO to cause an allergic reaction to those exposed due to the transgenes will not be considered further.

161. 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.

162. 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*

163. 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*

164. 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, 2.4.2 & 3.1.1 this Chapter).

165. In the context of the activities proposed by the applicant and considering both the short and long term, one of the three risk scenarios was considered 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	Adverse immune response Vaccinia-like disease, including serious adverse reactions Cancer particularly haematological malignancy progression	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 for enriched replication in cancer cells and less efficient replication in healthy 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. • Personnel conducting dealings would be offered smallpox vaccination • 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.

Risk scenario	Risk source	Causal Pathway	Potential harm	Substantive risk?	Reasons
2	GMO	i. Trial participant injected/infused with the GMO ⬇ ii. The GMO is shed at the infusion sites 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	Adverse immune response Vaccinia-like disease, including serious adverse reactions Cancer particularly haematological malignancy progression	yes	This risk scenario is considered substantive because there is a plausible pathway to harm. See detailed risk characterisation in Section 3.1.1
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 another virus in the host ⬇ iv. Produces a replication competent recombinant virus	Novel disease in humans Establishment of novel virus with unknown pathogenicity in the environment	No	• Participant having received a poxvirus-based treatment will be excluded from the trial. This reduces the likelihood of similar genomic sequences that are available for recombination. • Clinical trial participants 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 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	Exposure of people undertaking dealings in clinical trial facilities to GMO via: ▪ needle stick/ sharps injury/ eye splash during GMO preparation, administration, collection or analysis of samples ▪ GMO contact with abraded skin ▪ contact with GMO contaminated materials ⬇ Transduction of cells ⬇ Expression of immunomodulatory transgenes
Potential harm	Adverse immune response Vaccinia-like disease, including serious adverse reactions

Risk source

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

Causal Pathway and likelihood

167. There are several ways people may be exposed to the GMOs while undertaking the dealings as part of this trial. The GMO would be prepared and infused into clinical trial participants with solid tumours. Biological samples, including blood, anogenital and injection site swabs, and urine would be collected by trained staff throughout the trial.

Exposure via needlestick injury or handling of samples

168. During dealings involving preparation and administration of the GMO and sample collection, there is a potential risk of exposure to people involved in the trial via needle stick, sharps injury and/or eye splash. 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 IV bag. An eye splash might occur if either a vial containing the GMO or the IV infusion bag used for administration is perforated or dropped.

169. The use of PPE (e.g. gown, gloves, mask and eye protection) would minimise the potential for exposure of staff handling the GMO within the trial site. These samples may be prepared and analysed at the trial site or shipped to pathology laboratories. Controls proposed by the applicant, including appropriate training and the use of containment equipment, would considerably limit the risk of exposure via this route. Analyses of samples outside the trial site 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. These practices would prevent the exposure of personnel to the GMO. Additionally, appropriate decontamination and disposal practices would prevent persistence and spread of the GMO further reducing the likelihood of inadvertent exposure.

170. 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 people and animals.

171. The applicant has proposed that individuals who are pregnant or immunocompromised be excluded from undertaking dealings with the GMO.

Exposure via contact of abraded skin with infusion site

172. 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 a clinical trial participant's treatment, they could be exposed to the GMO.

173. Transmission of VACV from the treated trial participant to another person would require close contact with abraded skin. The applicant has stated that the IV line would be flushed with sterile normal saline after administration and that the infusion site would be coved by an occlusive dressing until healed. In addition, clinical trial staff would be wearing PPE. Together, these measures would limit the dissemination of the GMO from the infusion site and limit the potential for exposure of clinical trial staff to the GMO.

Exposure by contact with contaminated materials

174. People in clinical trial facilities could come in contact with GMO contaminated materials. 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.

175. Given the measures in place to protect personnel, including PPE, it is considered highly unlikely that personnel conducting dealings would be exposed to the GMO.

176. In the event of exposure, the GMO is designed for enriched replication in cancer cells and their destruction, and its replication is less efficient in healthy cells. It is expected to be rapidly cleared by the immune response in healthy individual. High-risk personnel will be excluded from handling the GMO. Therefore, the GMO is unlikely to spread systemically in individual engaged to conduct the trial.

Potential harm

177. If people undertaking dealings in clinical trial facilities are exposed and the GMO spread systemically, they could suffer from symptoms of VACV infection, and on rare occasions, an adverse immune response may occur such as those described in Section 3.1.

178. The personnel would be offered smallpox vaccination prior to conducting dealings. Smallpox vaccination will enable an individual with a competent immune system to mount a rapid and effective immune response to the GMO, preventing systemic infection, viral replication and transgene expression.

179. The vaccinia strain used to create the GMOs can replicate in human cells and cause illness in humans (Chapter 1, Section 3). However, the GMO has been modified by the removal of three genes, to have poor replication efficiency in healthy cells and preferentially replicate in cancer cells (Chapter 1, Section 4). In addition, the inserted IL-15 SA stimulates the host immune response. The combination of these changes increases the ability of the host to clear the virus. 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). 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 a transient reaction.

180. Individuals with underlying skin conditions, particularly atopic dermatitis, may be more susceptible to adverse effects following exposure. The pathophysiology of these conditions, including impaired skin barrier function, epidermal hyperplasia and dysregulated immune responses, can facilitate the systemic spread of poxvirus infection and increase the potential for serious adverse outcomes (Reed et al., 2012). The severity of this reaction would be mitigated by smallpox vaccination, if received, as well as medical treatment post GMO exposure that may be offered if deemed necessary, This would include VIG.

181. Staff conducting dealings may be unaware they have a developing cancer. As mentioned in section 4, although used to treat cancer, there are reports that IL-15 may promote cancer progression. However, if a staff member is exposed to the GMO, the exposure would be documented and reported, and the individual would undergo medical assessment and monitoring for at least 21 days following exposure. For higher-risk exposures, such as needlestick injuries, effective antiviral treatment may also be offered. These measures would enable early detection of GMO replication, allowing timely medical intervention if necessary.

182. Persistent overexpression of IL-15 SA could potentially result in adverse effects; however, the likelihood of such effects occurring would be substantially reduced by rapid clearance of the GMO by a vaccine-primed immune system (in the case of staff who opted for the smallpox vaccinations which are proposed to be offered by the applicant) and/or prompt medical intervention. Although CD55 may confer some capacity for immune evasion, once the GM VACV infects a cell, the enhanced immune activation mediated by IL-15 SA is expected to promote viral clearance. As a result, expression of CD55 is not expected to confer a net increase in viral persistence. In addition, the deletion of three viral genes further attenuates the GMO by enhancing host-mediated clearance of the virus from healthy tissues.

Conclusion

183. The potential for an unintentional exposure of people undertaking dealings in clinical trial sites to the GMO resulting in ill health in humans is not identified as a risk that could be greater than negligible. Therefore, it does not warrant further detailed assessment.

2.4.2 Risk scenario 3

Risk source	GMO
Causal pathway	Trial participant injected/infused with the GMO ⬇ Trial participant becomes or is already infected with another virus ⬇ The GMO recombines with another virus in the host ⬇ Produces a replication competent recombinant virus ⬇ Recombinant virus shed ⬇ 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

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

Causal Pathway

185. 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 infected with the GMO. If recombination occurs, the introduced genes could potentially restore the replication competence of the GMO. The resulting novel recombinant virus could then be more readily shed from its host.

186. 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).

187. 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.

188. 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. 274 cases of mpox have been detected in Australia this year (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).

189. 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.

190. 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.

191. The GMO is designed to preferentially localise to cancer cells and have poorer replication efficiency 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.

192. Finally, 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

193. 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.

194. 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 attenuate virulence and the inserted IL-15 SA will enhance the immune response. While the inserted CD-55 contributes towards immune evasion, the overall effect of the modifications would likely result in enhanced viral clearance.

Conclusion

195. The potential for an adverse outcome as a result of recombination between viruses is not identified as a substantive risk that could be greater than negligible. Therefore, it does not warrant further assessment.

Section 3 Risk characterisation

3.1.1 Risk scenario 2

Risk source	GMO
Causal pathway	Trial participant receives the GMO via IV ↓ GMO shed in bodily fluids, secretions or contaminated materials ↓ Another person is exposed to viable GMO particles ↓ Infection of susceptible cells ↓ GMO replication and expression of immunomodulatory genes
Potential harm	Adverse immune response Vaccinia-like disease, including serious adverse reactions Tumour progression

Risk source

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

Causal Pathway and likelihood assessment

197. After administration, the GMO could be shed from the clinical trial participants at infusion site, pustules that may form, or in bodily fluids. It could subsequently be transmitted to a person who came into close contact with either the trial participant, or a participant- generated fomite.

198. The GMO is administered via IV, leading to the presence of the GMO in the blood in the hours following administration. The GMO is expected to be cleared or be present at low levels for about 28 days as it is designed to stimulate the immune response and limited viral replication outside of cancer cells.

199. This would render transmission of the virus from clinical trial participants highly unlikely at 28 days and greater after administration. As applicant proposes 4 or more doses every 28 days, the exposure window for close contact is therefore a minimum of 112 days. Although it is expected that the GMO would be cleared more rapidly after each subsequent administration due to memory immune responses.

Exposure via contact with blood or body fluids

200. 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 individuals 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. Trial participants are excluded from participating in the clinical trial if they suffer from these conditions. This would reduce the likelihood of shedding in blood and urine, and therefore the likelihood of transmission to a close contact.

201. Furthermore, as per VACV vaccination, the administration of the GMO is expected to induce immunological responses capable of protecting against future infections. The acquired immune response, developed by the trial participant following multiple doses of the treatment, would limit the presence of the GMO in their body and body fluids. Additionally, trial participants would be instructed to use barrier contraception should they be sexually active during the treatment and for at least 60 days after the last GMO treatment. This measure would minimise the potential of transmission of the GMO via exposure to body fluids such as semen and vaginal secretion.

202. The effect of the GMO on a developing pregnancy is uncertain, however the applicant has proposed contraceptive measures be in place to prevent pregnancy.

203. The risk of exposure of healthcare staff during collection or analysis of biological samples was addressed in Risk Scenario 1 (Section 2.4.1).

204. The above-mentioned limits and controls would minimise the potential exposure of people to the GMOs via exposure to blood and bodily fluid. Close contact exposure to the GMO from bodily fluids is therefore **highly unlikely**.

Exposure via direct or indirect contact should trial participants develop pustules

205. The GMO could be transmitted from clinical trial participants if vaccinia-associated skin or oral pustules develop. Direct or indirect contact with pustules is the primary route of vaccinia virus transmission (Section 3.5). The attenuating viral gene deletions incorporated into the GMO enhance replication preferentially within tumour cells while limiting replication in normal tissues. As a result, the GMO is less likely than wild-type vaccinia virus to replicate extensively in healthy skin and form widespread pustular lesions. However, in participants with melanoma, the GMO may replicate efficiently in cutaneous tumour tissue, potentially leading to local lesion or pustule formation at tumour sites. Clinical trial participants may develop pustular lesions containing the GMO, particularly at the administration site.

206. Clinical trial participants would be informed of the risks associated with the GMO and instructed to follow hygiene and infection-control measures, including the appropriate management and disposal of contaminated dressings. Participants would also be required to keep any open lesions covered with occlusive dressings where there is a risk of contact with other individuals or shared surfaces. Trial participant would also be instructed to cover the administration site until healed. Where lesions occur on the genitalia, the use of barrier contraception would reduce the likelihood of transmission.

207. Direct contact with pustules, or indirect contact via contaminated fomites, may result in exposure to the GMO. Shedding from lesions may contaminate clothing, towels, dressings and bed linen. Consequently, close contacts of trial participants may be exposed to the GMO through contact with contaminated materials. Individuals who share a bed with a clinical trial participant are considered the most likely contacts to be exposed through this pathway because of the frequency and duration of contact with potentially contaminated bedding and any uncovered lesions/pustules.

Infection of susceptible cells in the exposed person

208. VACV is not readily transmitted between humans, with only limited evidence of secondary transmission reported during historical smallpox vaccination campaigns (Section 3.5). The attenuating modifications incorporated into the GMO reduce its capacity to infect and replicate in healthy cells, further decreasing the likelihood of transmission via shedding or pustule formation.

209. VACV infection most often leads to a localised infection at the exposure site. While the GMO parent strain can systemically disseminate, the viral attenuations make it difficult for disseminated virions to establish a systemic infection and would be susceptible to mechanism of immune clearance both innate and adaptive immune mechanisms that are not complement mediated.

210. Sustained GMO replication and transgene expression are expected to be limited by the tumour-selective nature of the GMO. The applicant states that efficient viral replication and robust transgene expression occur predominantly in tumour cells. Therefore, in individuals without susceptible tumour cells, the GMO is expected to be cleared by the immune system within approximately one week (Davies et al., 2017), limiting both the duration of infection and transgene expression. In the absence of susceptible tumour cells, it is **highly unlikely** for sustained GMO replication and transgene expression to occur. If susceptible tumour cells are present, rapid and sustained (up to 28days) viral replication together with high-level expression of the IL-15 SA transgene could occur.

211. The overall likelihood of this causal pathway is **highly unlikely**, as multiple unlikely steps would need to occur.

212. Individuals who are immunocompromised, pregnant, infants less than 12 months of age, people with active skin conditions, and the elderly are identified as at-risk groups by the applicant (paragraph 23) and would be at higher risk of infection and subsequent harm from the GMO. The applicant has stated that clinical trial participants would be instructed to avoid in-person contact or using shared spaces with at-risk people for 28 days post-treatment. Additionally, clinical trial participants with household contacts who are pregnant and/or breastfeeding are excluded from participating in the trial. As in-person contact and utilisation of shared-spaces would be avoided, it is **highly unlikely** that exposure to the GMO from trial participants to at-risk groups resulting in a sustained infection would occur.

213. As mentioned in Chapter 1, section 3.2, several species of domestic pets and livestock are susceptible to VACV infection and associated disease. The applicant has proposed that trial participants would be instructed to limit contact with household pets including avoiding close contact and sharing beds. The applicant has also proposed that clinical trial participants would be instructed to avoid contact with livestock particularly dairy cattle. These limitations would render the transmission pathway of shed GMO from the clinical trial participants to animals **highly unlikely**.

Potential harm

214. If people are exposed to the GMO, a range of outcomes are possible. The GMO is designed to replicate efficiently in cancer cells and has limited replication capacity in healthy cells.

215. In healthy individuals, the absence of cancer cells, any transduced healthy cells are expected to support little or no viral replication, allowing the GMO to be cleared by the immune system. The three deleted genes reduce replication competency and increase susceptibility to immune clearance (Section 4.1.2). While the CD55 inserted gene may enhance evasion of immune responses, the IL-15 SA stimulates immune activity, resulting in an overall effect that is not expected to prevent clearance in healthy hosts (Section 4.1.1). The modifications are expected to increase the likelihood of viral clearance following exposure of healthy individuals. Exposure would likely lead to asymptomatic infection or mild, self-limiting symptoms, although more pronounced acute reactions may occur in the event of higher-dose exposures. 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). Therefore, the potential outcomes for healthy individuals who are exposed to the GMO range from **minor** to **marginal** harm, requiring no or minor medical attention with no long-term harm.

216. In Individuals with pre-existing tumours, tumour cells provide a permissive environment for GMO replication and transgene expression. As described in detail in Section 4.1.1, IL-15 overexpression has been associated with both oncolysis as well as tumour progression. The applicant has demonstrated oncolytic activity of the GMO in solid tumour animal models, with anti-tumour effects considered to be mediated largely through IL-15-induced activation of immune effector cells, including T cells and NK cells. However, tumour responses to IL-15 are variable and depend on factors such as tumour type, cellular phenotype, receptor expression profile, IL-15 concentration and duration of exposure and the tumour microenvironment. Consequently, outcomes may range from tumour regression to no measurable effect or, in some circumstances, enhanced tumour survival or proliferation.

217. Individuals with haematological malignancies may be particularly susceptible to the biological effects of the IL-15 SA transgene. IL-15 promotes the activation, proliferation and survival of T cells and NK cells, a mechanism that is intended to enhance immune-mediated oncolysis. However, the same proliferative immune signals in tumours expressing IL-15 receptors, particularly T-cell lymphomas, may stimulate the proliferation and survival of tumours particularly cancerous T cells, potentially contributing to disease progression. Furthermore, individuals with haematological malignancies may have impaired immune function, which could reduce clearance of the GMO and prolong viral replication and transgene expression. This may increase the duration of exposure to the biological effects of both the GMO and the IL-15 SA transgene.

218. This could result in prolonged viral replication and sustained transgene expression, increasing the duration of exposure to the biological effects of both the GMO and the IL-15 SA transgene. Depending on

tumour-specific characteristics and the immune status of the affected individual, outcomes may range from immune-mediated oncolysis and tumour regression, to no measurable effect, to vaccinia-like disease, tumour progression or other adverse clinical outcomes. Given the substantial morbidity and mortality associated with haematological malignancies and other cancers, any GMO-mediated enhancement of tumour growth or disease progression could increase the need for medical intervention and, in severe cases, contribute to life-threatening illness or premature mortality. The applicant has proposed that clinical trial participants report signs of illness (including pustule development) in close contacts, including signs of infection, presence of lesion or pustules. This would allow for early detection of a systemic infection in a close contact and monitor and potentially treat a person exposed.

219. Therefore, the potential outcomes associated with GMO replication and transgene expression in individuals with susceptible tumour cells range from **minor** harm (Minimal or no increase in illness to people) to **major** harm, in the event early detection and treatment is not sufficient to treat an exposed close contact. In this extreme circumstance, exposure could result in life-threatening illness.

Risk estimate

220. For people without health issues, exposure to the GMO leading to clinical disease is a **highly unlikely** event of **marginal to minor consequence**, the estimate of risk to healthy people may be considered **negligible** (*risk is of no discernible concern and there is no present need to invoke actions for mitigation*).

221. For vulnerable people, exposure to the GMO leading to serious or life-threatening illness is a **highly unlikely** event of **minor to major** consequence, the estimate of risk to people exposed to the GMO may be considered **negligible** (*risk is of no discernible concern and there is no present need to invoke actions for mitigation*) to **moderate** (*risk is of marked concern and will necessitate actions of mitigation that need to be demonstrated as effective*).

Section 4 Uncertainty

222. 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.

223. 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 estimate the level of risk, the Regulator will take this uncertainty into account in making decisions.

224. 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.

225. For DIR-232, uncertainty is noted in relation to:

- the enriched replication of the GMO in cancer cells over healthy cells
- shedding of the GMO in humans
- the effect of the transgenes *in vivo*.
- the effect of the GMO on haematological malignancies

226. As this is a first in human trial, several pre-clinical studies in a mouse model have been conducted. These data are declared as CCI. Given that the applicant's pre-clinical 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.

227. 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 degree of uncertainty regarding its behaviour following infection. However, 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.

228. As an oncolytic virus, the GMO may have the capacity to lyse tumour cells. Oncolytic viruses for the treatment of haematological malignancies are under development, including candidates based on VACV (Yang et al., 2021). Therefore, it is possible that replication of the GMO within malignant cells could result in oncolysis, and a reduction in tumour burden. However, no data have been provided to demonstrate that the GMO has oncolytic activity against haematological malignancies. Oncolytic viruses developed for the treatment of solid tumours or haematological malignancies are tailored to the biological characteristics of their target cancer type (Xu et al., 2024; Yang et al., 2021).

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

230. 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.

231. Chapter 2, Section 4, discusses information that may be required for future release.

Section 5 Risk evaluation

232. 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 would be authorised, need further assessment, or require collection of additional information.

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

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

234. Three risk scenarios were postulated whereby the proposed dealings cause harm to people or the environment. Risk scenario 2 was identified as a substantive risk. The principal reasons for this conclusion include:

- the GMO is replication-competent making transmission from clinical trial participants to close contacts plausible
- the prolonged exposure window due to multiple doses
- systemic infection in vulnerable persons could contribute to vaccinia-like disease, tumour progression and poorer clinical outcomes.

235. Risk scenarios 1 and 3, in the context of the limits and controls proposed by the applicant, and considering both the short and long term, were considered to be negligible. The principal reasons for these conclusions are summarised in Table 1 and include:

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

236. While two of the 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, one risk scenario was estimated to be negligible to moderate. The Risk Analysis Framework (OGTR, 2013), which guides the risk assessment and risk management process, defines moderate risks as risks of marked concern that necessitate actions

for mitigation that need to be demonstrated as effective. Therefore, additional controls are required to treat this moderate risk. The additional controls are detailed in Chapter 3 as risk treatment measures and are considered adequate to manage the moderate risks identified in risk scenario 1. Hence, the Regulator considers that the dealings involved in this proposed release do not pose a significant risk to either people or the environment.

Chapter 3 *Risk management plan*

Section 1 Background

237. 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.

238. 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.

239. 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.

240. 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

241. The risk assessment of risk scenarios listed in Chapter 2 concluded that there was one substantive and two 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 specific risk treatment measures are required to treat the substantive risk.

242. To manage the substantive risk identified in scenario 2 (Section 3) to close contacts with haematological malignancies the following risk treatment measures are proposed.

- Individuals with cancer including haematological malignancies would be added to the defined class ***'Vulnerable persons'*** who clinical trial participants must be instructed to avoid close contact and shared spaces with. This reduces the likelihood that the clinical trial participant will expose individuals with cancer to the GMO. Licence conditions have been proposed to this effect.
- Clinical trial participants must follow specified hygiene and wound-care measures to minimise the risk of GMO transmission, including hand hygiene, occlusive dressings, cleaning of potentially contaminated items and surfaces, and preventing contact with infusion sites, lesions, pustules, dressings and contaminated materials. Participants must safely contain and return GMO-contaminated biohazard waste to the clinical trial site for disposal and promptly report any suspected exposure of another person or animal to the GMO. Licence conditions have been proposed to this effect.
- The applicant proposed the clinical trial participants report any unusual symptoms, including signs of infection, development of lesion and pustule, in close contacts to the clinical trial team. A licence condition is proposed which requires the applicant to directly inform close contacts of the risks associated with exposure to the GMO, particularly for undiagnosed haematological malignancies,

and to provide information on symptoms of concern, reporting pathways and health monitoring arrangements.

243. Together, these risk treatment measures effectively mitigate the substantive risk identified in the RARMP by greatly reducing the likelihood of exposure of vulnerable persons to the GMO and reducing the likelihood of significant harms being caused as a result of exposure to the GMO.

Section 3 General risk management

244. 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 identified in risk scenarios 1 and 3 posed to people and the environment are negligible. Therefore, to maintain the risk context, licence conditions have been proposed 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. Additionally, a range of controls to restrict the spread and persistence of the GMOs and their genetic material in the environment have been proposed. The conditions are discussed and summarised in this Chapter and listed in detail in the licence.

3.1 *Limits and controls on the clinical trial*

245. Sections 2.1 and 2.2 in Chapter 1 list the limits and controls proposed by Avance Clinical Pty Ltd. 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 Avance Clinical Pty Ltd

246. The proposed clinical trial would involve a limited number of 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.

247. The applicant advised that import and transport of the GMO and waste containing the GMO would be in accordance with IATA shipping classification UN 3245 [Category B] and/or the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*. These are standard protocols for the handling of GMOs 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.

248. 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.

249. The applicant has proposed inclusion and exclusion criteria for both trial participants and staff which are listed in Chapter 1, Sections 2.3.5and 2.6. 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 immunosuppressed individuals, children under 12 months of age and those with skin disease; such groups are also excluded from VACV vaccination. The applicant has proposed to exclude individuals with active autoimmune disease, active clinically significant infection, pregnancy or breastfeeding, active

eczema or a history of severe eczema, and ongoing severe inflammatory skin conditions from being enrolled as a clinical trial participant. This also minimises the potential for spread and persistence of the GMO as people in these groups are more likely to experience a serious adverse reaction. Accordingly, these groups are included in the definition of ***'Vulnerable persons'*** in the draft licence, and proposed conditions preclude their participation in the trial.

250. The applicant advised that the GMO would be administered to trial participants via IV 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 licence conditions.

251. The applicant proposed to prepare the GMO in a BSC II and that staff preparing and administering the GMO wear face masks. As discussed in paragraph 74 and paragraph 159, aerosols are not considered as a plausible pathway for exposure to the GMO. Therefore, the use of a BSC II and face masks have not been included in the licence conditions.

252. Conditions are proposed in the licence which would require 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.

253. 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 3.7) and compatible hosts such as rodents, marsupials and others as listed in paragraph 67 would be present in the Australian environment, disposal measures such as burial or maceration would not ensure containment. Therefore, proposed licence conditions require 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.

254. The applicant has proposed to provide clinical trial participants with instructions for the management of suspicious skin pustules and for good hand hygiene practices. Clinical trial participants would be provided with dressings, biohazard bags and a disposal container for contaminated dressings, reducing the likelihood of exposure of people and animals to the GMO. The applicant has also stated that the trial participants would be instructed to launder sheets and clothing in a bleach solution, and separately to other laundry, should pustule(s) develop.

255. Part of the applicant's proposed risk management plan is for the trial participants to be instructed to avoid at-risk individuals (paragraph 23). These vulnerable groups, which include children under 12 months of age, persons with recurrent or active skin conditions, persons who are pregnant or breastfeeding, immunocompromised and the elderly, are at greater risk of harm by VACV. As such, licence conditions are proposed that trial participants be instructed to avoid direct physical contact with vulnerable individuals for 28 days from the time of each treatment with the GMO or any time lesions are present.

256. 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 proposed in the licence to reflect this.

257. The applicant proposed that trial participants would be instructed to use contraceptives to avoid pregnancy during the clinical trial treatment for at least 90 days after the last treatment dose. As mentioned above, vaccinia virus shedding is mostly undetectable 28 days after inoculation. However, given the potential for harm if a pregnancy were impacted by infection with the GMO, a licence condition stipulating the use of barrier contraception for 60 days following the final treatment has been proposed. There is limited data regarding the shedding of the GMO in body fluids. Therefore, barrier contraception is

recommended to avoid exposure to the GMO via shedding in body fluids such as semen and vaginal secretions, in addition to prevention of pregnancy.

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

259. The applicant has proposed that trial participants limit contact with domestic pets and livestock. This measure would prevent transmission of the GMO to susceptible species and is therefore proposed as a licence condition.

260. Other conditions included in the draft licence are standard conditions stating 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.

261. 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 proposed to limit and control the clinical trial

262. Licence conditions have been included to limit and control the proposed clinical trial, based on the above considerations. These include requirements to:

- limit the number of trial participants,
- trial only 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
- require the offering of smallpox vaccination to personnel conducting dealings with the GMO and close contacts of trial participants
- require decontamination of the GMO and materials and equipment that have been in contact with the GMO at clinical trial sites using effective disinfectants
- require 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 3245 [Category B] and/or the minimum requirements for packaging, and labelling as detailed in the licence.
- clinical waste stream to be used by external service providers to destroy GMO-related waste.

3.1.3 Other risk management considerations

263. All DIR licences issued by the Regulator contain 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.

3.1.4 Applicant suitability

264. 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.

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

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

3.1.5 Contingency plans

267. Avance Clinical Pty Ltd 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.

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

268. Persons covered by the licence are the licence holder and employees, agents or contractors of the licence holder and other persons who are, or have been, engaged or otherwise authorised by the licence holder to undertake any activity in connection with the dealings authorised by the licence. Prior to dealings with the GMO, Avance Clinical Pty Ltd 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.

3.1.7 Reporting requirements

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

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

270. Written notices are 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.

3.1.8 Monitoring for compliance

271. 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.

272. 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.

273. 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

274. 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 obtained from testing in humans including:

- selective/preferential replication in cancer cells,
- tissue tropism,
- shedding of the GMOs in inoculated trial participants,
- effect of the GMOs and transgenes on haematological malignancies and solid cancers

Section 5 Conclusions of the consultation RARMP

275. The risk assessment concludes that the proposed clinical trial of the GMO poses negligible to moderate risks to the health and safety of people or the environment as a result of gene technology. The moderate risk requires specific risk treatment measures outlined in Section 2.

276. Conditions are proposed 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 risk

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.

'Close Contact' members of the same household, intimate partners or carers outside of the clinical trial site of the clinical trial participants.

'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 have an active autoimmune disease;

   (b) persons who are pregnant or breast-feeding;

   (c) persons who have household contacts who are pregnant;

(d) persons who have an active eczema or a history of severe eczema;

(e) persons who have ongoing severe inflammatory skin conditions;

(f) persons who have active and clinically significant infections (bacterial, viral, or fungal) including known hepatitis B virus, known hepatitis C virus, known HIV or AIDS or related illness;

'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.

'Vulnerable persons' means:

a) persons who are immunosuppressed;
b) persons who are breastfeeding or who are pregnant;
c) infants;
d) persons who have an active skin condition; including eczema, atopic dermatitis, or other conditions causing breaks in the skin barrier;
e) persons with cancer including haematological malignancies.

Section 2 General conditions and obligations

Holder of licence

3. The licence holder is Avance Clinical Pty Ltd.

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 proposed 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 applies 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 39(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 limited number of clinical 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 45(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 method(s) to prevent pregnancy and exposure to the GMO during sexual activities for at least 60 days after 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;

(d) remain at the clinical trial site until 4 hours post- administration;

(e) avoid direct physical contact and shared spaces with Vulnerable persons as defined in this licence, for at least 28 days after each treatment or any time pustules or skin lesions are present;

(f) cover any pustules or skin lesions that are formed within 60 days of GMO administration with occlusive dressings until healed;

(g) cover the administration site with an occlusive dressing changed every 48 hours until healed;

(h) dispose of contaminated dressings into the container provided as per condition 26(b);

(i) follow the hygiene measures as per condition 30;

(j) avoid direct physical contact with livestock susceptible to VACV, for at least 28 days after each treatment or any time lesions are present;

Note: Cattle are particularly susceptible to VACV infection.

(k) avoid contact between domestic pets and the administration site, for at least 28 days after each treatment;

(l) provide their close contacts with information on the risks associated with exposure to the GMO and reporting mechanisms for any symptoms consistent with *vaccinia*.

30. The licence holder must instruct the clinical trial participants to follow 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 administration site, pustules, skin lesions 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 and/or pustules or skin lesions, including:

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

ii) ensuring persons caring for pustules or skin 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 pustules or skin lesions in a primary container (e.g. a press-sealed bag), placing these within a secondary container (e.g. a biohazard bag/container) 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 practicable if they suspect exposure of a person to a pustule or skin lesion has occurred.

31. The licence holder must ensure that each clinical trial participant is inspected for pustules and skin lesions by an authorised person during scheduled visits at the clinical trial site 7 days post administration following the first 3 administrations of the GMO. A record of the outcome of the inspection must be provided to the regulator on request.

Conditions related to the conduct of the dealings

32. 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.

33. 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.]

34. 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

35. For the purposes of Condition 33 work practices and behaviours within a Clinical trial site must include, but are not limited to, the following:

(a) prior to conducting dealings, persons conducting the dealings must be informed of additional risks to those who are immunosuppressed, pregnant, have a cancer and/or haematological malignancies or active skin disease;

(b) prior to conducting dealings, persons conducting dealings with the GMO must be offered smallpox vaccination if available, and the offer recorded in the individuals signed statement;

(c) persons preparing and administering the GMOs must be suitably qualified and trained staff in conducting dealings with the GMOs;

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

(e) 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;

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

(g) equipment used for dealings with the GMOs must be decontaminated after use;

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

(i) the initial dressing applied to the administration site must be removed, the administration site cleaned and a new occlusive dressing applied prior to the trial participant leaving the Clinical trial site.

Transport, storage and disposal of the GMOs

36. 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.

37. 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].

38. 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.

39. The licence holder must ensure that transport and storage of the GMO, unless conducted according to Condition 37 or 38, 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 39(a)iii), 3939(a)iv) and 39(c) do not apply.

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

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

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

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

41. Where transport is conducted by External service providers for the purpose of destruction, the licence holder must ensure that the GMO, or waste reasonably expected to contain the GMO, 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

42. 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.

43. 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 proposed 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****.*

44. 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.

45. 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, 46 and 47;

    (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 33 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.

46. 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.

47. 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.

48. 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.

49. 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: 232

Title: Clinical trial of an IV administered GM vaccinia virus in subjects with advanced solid tumours

Organisation Details

Postal address: Avance Clinical Pty Ltd
Level 22, 91 King William Street
Adelaide
South Australia, 5000

Phone No: (+61 8) 8249 4788

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 CLD-401 is a live vaccinia virus treatment derived, modified to preferentially replicate in tumour 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:	
CD-55-A33R (human immune gene and vaccinia outer envelope gene)	Expression of chimeric A33R+CD55 fusion protein, protects the GMO against completement mediate neutralisation.
IL-15 SA (genetically modified human immune gene)	Expression of IL-15 SA. Activation of NK and CD8+ T cells in the participant enhancing anti-tumour immune responses.
Deleted VACV genes:	
VGF	Complete loss of VGF leading to viral attenuation
JR2	

A46R	Complete loss of thymidine kinase activity leading to preferential tumour replication Complete loss of A46 protein leading to viral attenuation

Trial participants and route of administration of the GMOs

Intravenous administrations to adult humans with solid tumours.

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	44	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, 46 and 47; (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 33 will be achieved in relation to preparation of participant Samples for analysis subsequent to administering the GMO.	45	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.	46	30 days after final dose or discontinuation of participation
The licence holder must inform the Regulator as soon as reasonably possible:	47	Immediately

(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.		
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	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.	49	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
A record of the outcome of the inspection of the trial participant for the presence in pustule must be provided to the regulator	31	Upon request

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