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BUILDING
A HEALTHY
AUSTRALIA

Gain-of-Function Research Review Report

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NHMRC

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E: nhmrc.publications@nhmrc.gov.au
P: (02) 6217 9000

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Definitions

For the purposes of this Report, terms are defined as outlined in **Table 1**.

Table 1. Definitions

Term	Definition
Attenuation	Diminution of virulence in a strain of an organism, obtained through selection of variants that occur naturally or through experimental means.[1]
Biological entity	A living organism such as an animal, insect, plant, virus, bacterium or fungus.
Biosafety	The containment principles, technologies and practices that are implemented to prevent the unintentional exposure to biological agents and toxins, or their inadvertent release.[2]
Biosecurity	Principles, technologies and practices that are implemented for the protection, control and accountability of biological materials and/or the equipment, skills and data related to their handling. Biosecurity aims to prevent their unauthorised access, loss, theft, misuse, diversion or release.[2]
Containment	The combination of physical design parameters and operational practices that protect personnel, the immediate work environment and the community from exposure to biological agents.[2]
Dual-use research	Research that is intended to provide a clear benefit, but which could easily be misapplied to do harm. It may refer to work in the life sciences, but the principles are also applicable to other fields including engineering and information technology. It encompasses everything from information to specific products that have the potential to create negative consequences for health and safety, agriculture, the environment or national security.[3,4]
Gain of function	The acquisition of a new, or enhancement of an existing, characteristic/function (phenotype) of a biological entity due to the modification of its genetic material (genome).[5,6,7,8,9,10] Changes to the genome may occur spontaneously in nature or may be directed through experimental manipulations in a laboratory.[9,11]
Gain-of-function research	A type of research where the experimental manipulation results in gain of function (see definition above).[12]
Gain-of-function research of concern	A subset of gain-of-function research that could increase the harmfulness of an infectious agent to humans.
Gene	A specific sequence of nucleotides in DNA or RNA that is the functional unit of inheritance and is usually located on a chromosome.[13]
Genome	The entire genetic material of an organism, made out of DNA (or RNA in some viruses).[14]
Genotype	An organism's version of a nucleotide sequence.[15]
Infectious agent	A biological agent that causes disease or illness to its host (humans, animals or plants). Also called a pathogen or germ. Most infectious agents are microorganisms (such as bacteria, viruses, fungi and protozoa), parasites and prions. However, not all microorganisms are infectious agents, e.g. 'good' bacteria present in the body's normal flora.[16]
Infectious disease	A type of illness caused by an infectious agent.[17]
Institution	Any organisation that is involved with the conduct of research including universities, hospitals, research institutes, government departments or agencies, agricultural organisations, commercial companies, and organisations involved in animal breeding and supply.

Term	Definition
Life sciences	The sciences concerned with living things such as biology, botany and physiology.[18]
Microorganism	A living thing that is too small to be seen with the naked eye. Examples of microorganisms are bacteria, viruses, fungi, algae, protozoa, and microscopic animals such as the dust mite.
Notifiable disease	A disease where an outbreak of the disease is considered to be a public health risk.[19]
Oncogene	A mutated gene that contributes to the development of a cancer.[15]
Organism	A living being that can reproduce, grow, react to external stimuli and maintain its internal equilibrium.[17]
Pandemic	An epidemic occurring worldwide, or over a very wide area, crossing international boundaries and usually affecting a large number of people.[20]
Pathogen	See 'infectious agent'.
Pathogenicity	Ability to cause disease.[21]
Pathogen with pandemic potential	A pathogen that satisfies both of the following: 1. It is likely highly transmissible and likely capable of wide and uncontrollable spread in human populations. 2. It is likely highly virulent and likely to cause significant morbidity and/or mortality in humans.[22]
Phenotype	An observable trait in an organism. Phenotype can refer to anything from a common trait, such as height or hair colour, to the presence or absence of a disease. The genetic contribution to the phenotype is called the genotype. Some traits are largely determined by the genotype, while other traits are largely determined by environmental factors.[15]
Prion	Proteinaceous infectious particles that lack nucleic acids, which can cause scrapie and other related neurodegenerative diseases of humans and animals.[23]
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2. The scientific name of the coronavirus that causes COVID-19.
Security Sensitive Biological Agents (SSBAs)	Biological agents (including toxins) that are included in the List of SSBAs established by the Australian Government Minister for Health and are considered to be of security concern to Australia. SSBAs could be developed, produced, stockpiled, acquired or retained in types and quantities that could allow the agent to be used as a weapon and are therefore regulated.[24]
Transmissibility	The extent to which an infectious disease or a genetic disorder trait is able to be passed from one person or organism to another.[1]
Viral vector	A virus that has been modified so that it is unable to cause disease and is used to deliver genetic material into cells.
Virulence	The capacity of any infectious organism to cause disease and to injure or kill a susceptible host.[1]
Zoonotic disease (zoonosis)	Infectious disease that is naturally transmitted from animals to humans and vice versa.[2]

Abbreviations

Abbreviations used in this report are outlined in **Table 2**.

Table 2. Abbreviations

Abbreviation	Meaning
AEC	Animal Ethics Committee
ACDP	Australian Centre for Disease Preparedness
ACIAR	Australian Centre for International Agricultural Research
ANZ Standard	Australian/New Zealand Standard *Safety in laboratories. Part 3: Microbiological safety and containment* (AS/NZS 2243.3:2010)
ARC	Australian Research Council
BSC	Biological safety cabinet
BSL	Biosafety level
COVID-19	The coronavirus disease caused by the virus SARS-CoV-2
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CSIRO	Commonwealth Scientific and Industrial Research Organisation
DAWE	Department of Agriculture, Water and the Environment
DESE	Department of Education, Skills and Employment
DFAT	Department of Foreign Affairs and Trade
DISER	Department of Industry, Science, Energy and Resources
DNA	Deoxyribonucleic acid
DoH	Department of Health (Commonwealth)
DSGL	Defence and Strategic Goods List
GMO	Genetically modified organism
GoF	Gain of function
GoFR	Gain-of-function research
HREC	Human Research Ethics Committee
IBC	Institutional Biosafety Committee
NHMRC	National Health and Medical Research Council
OGTR	Office of the Gene Technology Regulator
PC	Physical Containment
PPP	Pathogen with pandemic potential
RNA	Ribonucleic acid
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SSBA	Security Sensitive Biological Agent
TGA	Therapeutic Goods Administration
UA	Universities Australia
WHO	World Health Organization
WHS	Work health and safety

Executive summary

At the request of the Minister for Health and Aged Care, the Hon Greg Hunt MP, the National Health and Medical Research Council (NHMRC) has undertaken a review of gain-of-function research. The Gain-of-Function Research Review reports on:

- the definition of gain-of-function research, the uses and benefits of such research, as well as how research of this nature could pose a threat to human health
- the framework for the regulation and oversight of research in Australia, with a focus on those aspects of the framework that ensure the safe, responsible and ethical conduct of research, including gain-of-function research
- gain-of-function research that has been funded by the Australian Government, or conducted by a Government agency, over the last 10 years and that could increase the harmfulness of an infectious agent to humans (also called gain-of-function research of concern)
- how the regulatory framework that controls such research in Australia compares internationally, with a focus on the management of biosafety and biosecurity risks.

The terms of reference for the review are outlined at **Appendix A**. The terms of reference do not include investigating the origin of the SARS-CoV-2 virus responsible for the COVID-19 pandemic.

The review involved consultation with, and collection of information from, Australian Government agencies, including those that fund or conduct life sciences research and that are responsible for the regulation of such research (**Appendix B**).

What is gain-of-function research?

'Gain of function' is a general term. For the purposes of this review, it is used to describe a change to the genome of any biological entity – a living organism such as an animal, insect, plant, virus, bacterium or fungus – through any process so that it acquires a new or enhanced function. Changes to the genome may occur spontaneously in nature or as the result of an experimental manipulation in a laboratory.

Gain-of-function research is a type of research where the manipulation of the genome results in a gain of function. Investigating gain of function is a powerful experimental approach that is routinely used in life sciences research, including genetic, biological and microbiological research. It involves a broad range of experimental techniques that have been used for many decades.

The use of 'gain of function' in this report reflects the wide-ranging occurrence of gain of function in nature and an experimental approach used in a broad range of scientific disciplines. Recently, the term has been used to refer to its application in research involving infectious agents and, more specifically, viruses. However, limiting the definition of gain of function to these types of research represents only a part of its application.

Most gain-of-function research is safe and leads to many benefits for human health. Gain-of-function research has led to new knowledge and technologies, including:

- new knowledge about how biological systems work and the processes underlying human and animal health and disease
- new knowledge about how infectious agents spread, infect and cause disease
- new pharmaceuticals and vaccines, precision medicine and gene therapies.

Concerns about some gain-of-function research

Gain-of-function research can be 'of concern' if it changes the characteristics of an infectious agent in a way that could increase the risk of harm to humans. Such research is generally performed to study a particular infectious agent and to develop strategies and technologies to prevent, detect or treat human infection by the agent.

This type of research has also been described as 'gain-of-function research of concern' and was the focus of this review.

A range of additional characteristics (gain of function) may be conferred on an infectious agent that could increase its harmfulness to humans, such as:

- enhanced production of the infectious agent (e.g. increased replication cycle or growth)
- enhanced morbidity (illness) and mortality (death)
- enhanced transmissibility (how easily it spreads) and host susceptibility
- evasion of existing natural or induced immunity
- resistance to drugs or evasion of other medical countermeasures such as vaccines, therapeutics or diagnostics.

Concerns about gain-of-function research have led to calls to ban such research, especially where it involves infectious agents with pandemic potential. An infectious agent with pandemic potential is one that is highly transmissible and capable of wide and uncontrollable spread in human populations, and highly virulent and likely to cause significant morbidity and/or mortality in humans. In a very small subset of gain-of-function research, characteristics may be conferred on an infectious agent that increase its pandemic potential or cause it to acquire pandemic potential. In the United States of America (USA), this has been called research involving 'enhanced potential pandemic pathogens' (enhanced PPP).

This review focused on identifying 'gain-of-function research that could increase the harmfulness of an infectious agent to humans', which includes but is broader than enhanced PPP. For the purposes of the review, this broader category is also described as 'gain-of-function research of concern'.

Australian regulatory framework

Research in Australia is expected to be conducted responsibly and be ethically justified. Biosafety or biosecurity risks must be identified and effectively mitigated and the potential for inadvertent or deliberate misuse of the research must be minimised.

Australia's framework for the regulation and oversight of research is comprehensive and aims to ensure the safe, responsible and ethical conduct of research. The framework includes a combination of Commonwealth and state/territory legislation, national standards and guidance, as well as local institutional governance and practices.

Controls applied to all life sciences research also apply to research that involves infectious agents, including potential gain-of-function research. These controls include ethics and safety approvals (including biosafety and biosecurity) from government bodies and/or institutional committees that encompass consideration of the risks and benefits of the research. There are additional controls for, and oversight of, research involving infectious agents and research involving genetically modified organisms (GMOs) including Commonwealth, and corresponding state and territory, biosecurity legislation and gene technology legislation.

Relevant approvals must be obtained before research commences. Monitoring and reporting requirements ensure that research is conducted in accordance with relevant licences and approvals. Monitoring and reporting also ensure that any issues that arise during the conduct of the research are detected and adequately addressed.

Gain-of-function research in Australia

Over the last 10 years, the Australian Government has funded or conducted 17 research projects that were identified in this review as gain-of-function research that could increase the harmfulness of an infectious agent to humans (also described as 'gain-of-function research of concern'). These projects comprise less than 0.3% of the more than 6000 infectious disease research projects that were funded or conducted by Australian Government agencies in the same period.

Of the 17 research projects identified, 10 were funded by NHMRC and 8 were conducted by the Commonwealth Scientific and Industrial Research Organisation (CSIRO); one project was both funded by NHMRC and conducted by CSIRO. Information about the projects is presented in general terms and, where appropriate, aggregated form. This approach is necessary to protect researchers from potentially serious threats to their personal and professional lives, as has been experienced by scientists around the world in the context of COVID-19.

Of the 17 research projects, 13 involved virological studies and 4 involved bacteriological studies. The research projects aimed to achieve benefits for human health including better understanding of viral and bacterial infections and how to detect, prevent and treat these infections. In all cases, the controls required under Australia's regulatory framework for the safe and ethical conduct of research, including biosecurity and biosafety, were in place. All projects were conducted in appropriate physical containment facilities with the required approvals or licences. The projects were monitored appropriately and there were no reported incidents involving infectious agents or GMOs during the conduct of the projects.

International comparisons

Australia's framework for the regulation and oversight of life sciences research is comprehensive and comparable to frameworks in other relevant countries. The comparability of Australia's framework with relevant international benchmarks is in part because of the adoption and harmonisation of international standards in many areas (e.g. research involving animals or human biospecimens, export controls and dual-use research).

In other areas, Australia's regulatory framework is more extensive than other countries. For example, unlike Canada and the USA, Australia has specific legislation for laboratory-based research with GMOs and the Gene Technology Regulator certifies facilities undertaking such research.

Australia's approach to health security has also been recognised internationally for its capabilities to prevent, detect and prepare for biosecurity and biosafety risks. Aspects of Australia's approach to biosecurity have also been used as the model for other countries and our biosafety requirements are recognised as establishing an organisational culture of safety in Australian laboratories.

Conclusion

The review report notes the many uses of gain-of-function research that have resulted in significant medical innovations and benefits to human health, and outlines the strong regulatory controls in Australia that ensure research is conducted safely, ethically and responsibly.

The Australian Government has funded and/or conducted a large volume of research on infectious agents that could cause disease in humans (including potential zoonotic animal diseases) over the last decade, contributing to Australia's considerable strengths in this field. The review found that the Government has funded through NHMRC, or conducted at CSIRO, gain-of-function research that could be categorised as 'of concern' because it

involved modifying a virus or bacterium in a way that may make it more dangerous to humans. This research aimed to increase understanding and improve the detection, prevention and treatment of a range of viral and bacterial infections.

Gain-of-function research in Australia is subject to best-practice biosafety and biosecurity controls that protect both the scientists undertaking the research and the Australian community. For example, Australia has a strong regulatory framework for the use of GMOs, which includes specific national legislation for laboratory-based research with GMOs and certification of facilities undertaking such research by the Gene Technology Regulator. Australia also has world-class physical containment facilities, including CSIRO's Australian Centre for Disease Preparedness (ACDP), which is a physical containment level 4 facility designed to allow scientific research on the most dangerous infectious agents to be performed safely. Australia's depth of expertise in infectious disease research and the availability of high-quality biosafety containment facilities enables the safe conduct of important research to prevent, detect and protect the Australian community from the threat of infectious diseases.

Introduction

'Gain of function' is a term used to describe a change to any biological entity – such as an animal, insect, plant, virus, bacterium or fungus – through any process so that it acquires a new or enhanced function. Certain gain-of-function experiments have raised concerns because of their potential to increase the danger posed to humans by an infectious agent, such as a virus. These concerns have been heightened by uncertainty about the origin of the SARS-CoV-2 virus responsible for the COVID-19 pandemic and suggestions that the SARS-CoV-2 virus may have been created in a laboratory as the product of gain-of-function research.

At the request of the Minister for Health and Aged Care, the Hon Greg Hunt MP, the National Health and Medical Research Council (NHMRC) conducted a review of gain-of-function research in Australia. The terms of reference for the review (**Appendix A**) require reporting on:

1. the definition of gain-of-function research, with particular reference to research of this nature that could pose a threat to human health
2. any gain-of-function research that could increase the harmfulness of an infectious agent to humans that has been funded or conducted by the Australian Government or its agencies over the last 10 years
3. the regulatory framework that controls such research in Australia, and how it compares with frameworks in other relevant countries.

The terms of reference do not include investigating the origin of the SARS-CoV-2 virus responsible for the COVID-19 pandemic. As the review is limited to the identification of gain-of-function research funded or conducted by Australian Government agencies (Term 2 above), the review did not consider any research funded or conducted solely by an overseas funding agency, a state or territory government or a private organisation.

The review involved consultation with other Australian Government agencies, including those that may have funded or conducted relevant research and that are responsible for the regulation of such research (**Appendix B**).

Structure of this report

This report is structured to address the terms of reference for the review.

- Part 1 outlines the definition of gain-of-function research, including detailing where research of this nature could pose a threat to human health (Term 1 in the terms of reference).
- Part 2 describes the framework for the regulation and oversight of research in Australia, including gain-of-function research (part of Term 3 in the terms of reference).
- Part 3 identifies gain-of-function research that could increase the harmfulness of an infectious agent to humans that has been funded or conducted by the Australian Government or its agencies over the last 10 years (Term 2 in the terms of reference).
- Part 4 compares Australia's framework for the regulation and oversight of research with other countries (part of Term 3 in the terms of reference).
- Parts 5 and 6 present the conclusions and provide additional information and references, respectively.

PART 1: Context

Part 1 provides the context for this review by describing the concept of 'gain of function', examples of research techniques used to achieve gain of function, and the uses and benefits of gain-of-function research (**Section 1: Background**) and by outlining the concerns over some gain-of-function research (**Section 2: Concerns about some gain-of-function research**). Section 2 also outlines how research in the life sciences can be categorised to identify gain-of-function research involving infectious agents that could increase the harmfulness to humans. This categorisation forms the basis of the methodology for the review (as further explained in **Part 3** of the report).

Key points

Background

- 'Gain of function' is a term used to describe a change to the genome of any biological entity – such as an animal, insect, plant, virus, bacterium or fungus – through any process so that it acquires a new or enhanced function. Changes to the genome may occur spontaneously in nature or as the result of an experimental manipulation in a laboratory.
- 'Gain-of-function research' is research where the manipulation of the genome of an organism results in 'gain of function'. This type of research is common in genetic, biological and microbiological research and has led to significant benefits for humans. The experimental manipulations used to change a genome include a range of fundamental techniques that have been used in research for many decades.
- Most gain-of-function research is safe and leads to many benefits for human health.

Concerns about gain-of-function research

- 'Gain-of-function research of concern' is used to describe the subset of gain-of-function research that could increase the harmfulness of an infectious agent to humans, including but not limited to research involving enhanced pathogens with pandemic potential.
- The risks of working with microorganisms, such as infectious agents, vary depending on their pathogenicity and transmissibility, and the availability of effective preventive measures and treatment. Gain-of-function research can be of concern if it changes the characteristics of an infectious agent in a way that could increase the risk of harm to humans.
- In a very small subset of gain-of-function research, characteristics may be conferred on an infectious agent during the conduct of the research that may increase its pandemic potential or cause it to acquire pandemic potential. An infectious agent with pandemic potential is one that is highly transmissible and capable of wide and uncontrollable spread in human populations, and highly virulent and likely to cause significant morbidity and/or mortality in humans.
- Research that is intended to provide benefit but could also inadvertently or deliberately be used to cause harm has been described as 'dual-use research of concern'. In life sciences research, some gain-of-function research involving infectious agents may be of concern because of its potential for dual use.

1. Background

This section explains the concept of 'gain of function' and how gain of function may occur, both naturally and as a result of experimental research in a laboratory. As it is based on terms used in genetics, a brief introduction to terms such as 'genome, 'gene' and 'DNA' is provided. This section also describes gain-of-function research, examples of fundamental research techniques used to achieve gain of function, and the uses of gain-of-function research.

1.1 Understanding the concept of gain of function

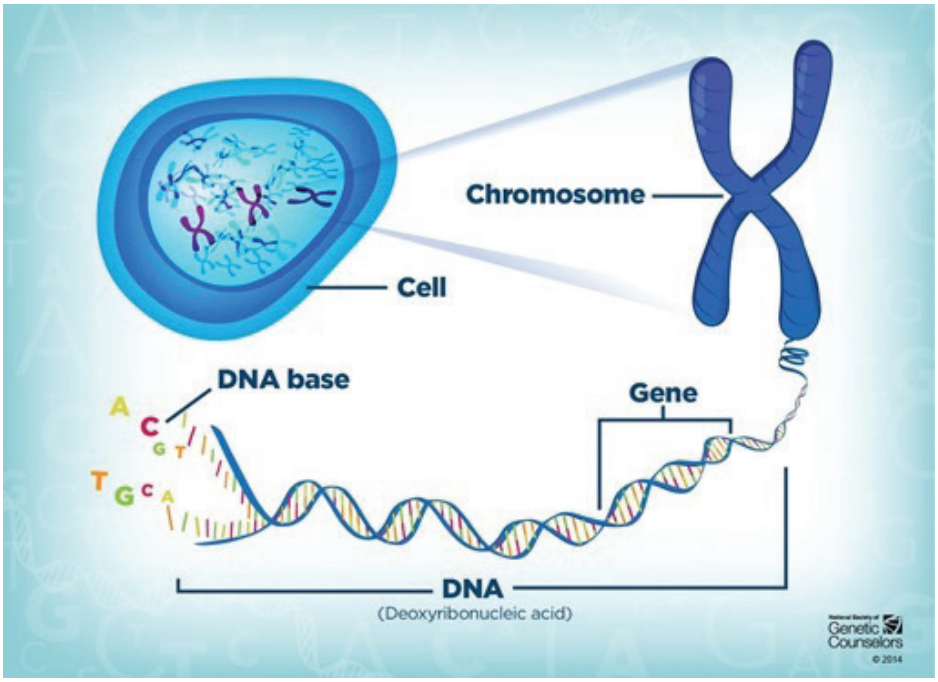
1.1.1 Underpinning concepts in genetics

In order to understand the concept of 'gain of function', it is important to understand the underlying biology. Every living biological entity (for example, an animal, insect, plant, virus, bacterium or fungus) has a unique genome, which is the organism's complete set of genetic material. It contains DNA (deoxyribonucleic acid), or RNA (ribonucleic acid) in the case of some viruses, which consists of a sequence of four different sub-units called nucleotides or DNA bases arranged in a particular order. DNA usually comes in a double strand forming the iconic double helix structure. It provides the instructions or code needed for an organism to develop, survive and reproduce. To carry out these functions, DNA sequences are used to make protein following a process of transcription (conversion of DNA to RNA) and translation (conversion of RNA to protein). Proteins are the complex molecules that help make up the structures of the organism (such as organs and tissues) and perform the myriad functions of the organism (such as chemical reactions and carrying signals between cells).

Each DNA sequence (or RNA sequence, in the case of RNA viruses) that contains instructions to make a functional molecule, including proteins, is known as a gene. The process of conversion of the DNA into proteins is known as 'gene expression' and is tightly regulated so that genes are expressed at the appropriate times and places and in the correct amounts. In the cells of humans, animals, plants and some other organisms, DNA is packaged into structures called chromosomes.

A useful analogy is to compare the genome to a book, where a chapter represents a chromosome, sentences in these chapters would be genes, the words would be DNA and the letters that make up each word would be the DNA bases that make up the DNA (**Figure 1**).[25,26,27]

Figure 1. Composition of the genome within a cell[25]

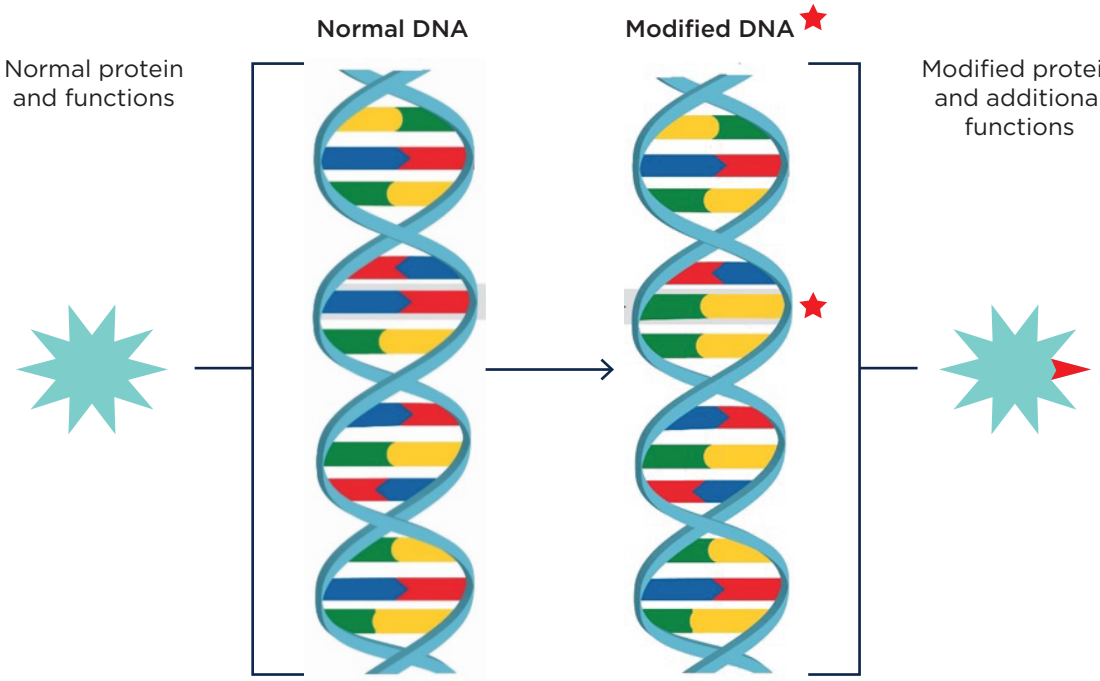


1.1.2 What is 'gain of function'?

When the genome of an organism (for example, an animal, insect, plant, virus, bacterium or fungus) is modified so that the organism acquires a new function or an enhancement of one of its existing functions, this is described as 'gain of function' (**Figure 2**). Changes to the genome may occur spontaneously in nature or may be directed through experimental manipulations in a laboratory.[9]

The different types of gain of function are further discussed in **Section 1.2**.

Figure 2. Gain of function associated with modified DNA. (Adapted[28,29])



The term ‘gain of function’ can have different meanings depending on the context and is not a standard term used in scientific publications. The definition of ‘gain of function’ in this report reflects the wide-ranging occurrence of gain of function in nature and an experimental approach used in a broad range of scientific disciplines. Recently, the term has been used to refer to its application in research involving infectious agents and, more specifically, viruses. However, limiting the definition of gain of function to these types of research represents only a part of its application.[30]

Modification of the genome of an organism, either spontaneously in nature or through experimental manipulations, can also lead to the organism losing all or part of an existing function. This is described as ‘loss of function’ and is not the focus of this review.

1.2 Types of gain of function

1.2.1 Spontaneously occurring gain of function

Mutations are alterations to the genome (including deletion, insertion or substitution of nucleotides) that may occur spontaneously.[31] Most of the time, the changes are small and may have no effect on functions. In some cases, a random change in the genome that arises by chance can confer some new function on a gene (**Figure 2**). [31,32]

For example, genetic changes or mutations in infectious agents occur frequently in nature. Some of these mutations can cause infectious agents to gain new functions or enhance existing functions, such as fitness (ability to survive and reproduce), transmissibility (how easily an infectious agent will spread from an infected person or organism to a susceptible person or organism), pathogenicity (ability to cause disease) or acquisition of resistance to treatments such as antibiotics. Although naturally occurring genetic mutations may be minor and random, accumulation over time can lead to new variants (for example, the Delta and Omicron variants of SARS-CoV-2) and sometimes a new strain of an infectious agent (for example, new strains of viruses, especially RNA viruses).[7,33] They may also lead to an infectious agent such as a virus evading selective pressure from the host immune response and adapting to changing environments, which may result in enhanced pathogenicity in a specific host. Many outbreaks in recent history have been attributed to viruses jumping from one host species to another; for example, influenza A viruses have jumped from birds and pigs to humans multiple times, the SARS epidemic in 2003 was caused by a species jump of coronavirus from bats and palm civets to humans, and HIV type-1 is believed to have switched hosts from non-human primates.[34]

Genetic changes or mutations also occur spontaneously in human cells. For example, the development of many cancers is driven by gain-of-function mutations that spontaneously occur in adult (somatic) cells leading to the growth and survival of abnormal cells.[35] An example is chronic myeloid leukaemia, which is caused when two chromosomes in a cell in the bone marrow break, exchange portions and fuse to create a new gene. This new gene is continuously activated and promotes the survival and growth of abnormal cells in the bone marrow.[36]

1.2.2 Gain-of-function research

Gain-of-function research is a type of research where the experimental manipulation of the genome of a biological entity results in a gain of function. Investigating gain of function is a powerful experimental approach that is routinely used in life sciences research, including genetic, biological and microbiological research.[6]

Gain-of-function research includes a range of fundamental techniques that have been used to alter the genome of an organism for many decades. Examples of these techniques are summarised below.

In silico technologies (that is, performed on a computer or via computer simulation) that can model and predict the functional consequences of gain-of-function mutations are not described in this report as these technologies do not produce a biological entity and are out of scope for this review.

Table 3. EXAMPLES: Experimental techniques used in gain-of-function research

Technique	What the technique involves	Examples of its use
Serial passage[37]	Repeated process of growing an organism (e.g. bacterium, virus) in one environment and then taking a portion of the population of the organism and growing it in a new environment (e.g. in the presence of a drug, in a particular cell type or animal model). The process leads to selection of spontaneously occurring mutations that promote increased survival and growth under the new conditions. The final product is studied, often in comparison with the original.	• Producing attenuated viral strains (i.e. with decreased virulence) or increasing viral yield for vaccine production. • Determining how an infectious agent acquires resistance to therapeutic agents such as antibiotics. • Using an animal model for understanding how a disease is caused by a bacterium or virus and for testing novel therapies.
Induced mutagenesis[38,39]	The artificial induction of DNA mutations at random within the genome of an organism. Methods include: • physical (e.g. ionising radiation) • chemical (e.g. alkylating agents) • insertional (e.g. using DNA sequences that can move from one location to another in the genome).	Improving our understanding of genetic factors affecting normal or disease processes. By altering a characteristic (phenotype) in an organism, through mutation, the genetic cause of that change can be examined.
Recombinant DNA technology[40,41]	The cutting and joining together of DNA molecules from different organisms, outside of the organisms. The recombined DNA molecule is inserted into a host organism to produce a new genetic combination.	Insertion of a human insulin gene into the genetic material of a common bacterium so that the bacterium can now produce the insulin encoded by the human gene. The bacterium is then grown and the insulin harvested for treatment of diabetic patients.
Gene editing[42]	The precise introduction of desired modifications to the DNA within a live organism. This has become a highly accessible technique due to the advent of CRISPR, a programmable set of 'molecular scissors' that can generate DNA breaks at specific sites within the genome. Gene editing may be considered a form of recombinant DNA technology.	• Introducing a modification into an organism's existing DNA to study the resulting protein's function and potential contribution to disease (reverse genetics). • Using CRISPR libraries (programmed to target large numbers of genes throughout the genome) for high-throughput screening of genes involved in a particular disease.
Synthetic biology[14,43]	The design and construction of biological parts, devices and systems, as well as the re-design of existing, natural biological systems for useful purposes. Redesigning organisms so that they produce a substance, such as a medicine or fuel, or gain a new ability, such as sensing something in the environment, are common goals of synthetic biology projects.	• Engineering entirely new proteins using computational design from chemically synthesised DNA. • Harnessing microorganisms to perform new functions (e.g. for bioremediation). • Modifying plants to express new proteins.

1.3 Uses and benefits of gain-of-function research

As outlined above, gain-of-function research encompasses a broad range of experimental approaches that are widely used to gain new knowledge across many areas of the life sciences. For more than 40 years, gain-of-function research has underpinned much new knowledge in basic science and about normal human biology and disease processes, our understanding of how pathogens work and the development of novel therapies. Gain-of-function research has also been critical to many Australian contributions to advancing human health.

Examples of some of the uses and benefits of gain-of-function research are outlined below.

1.3.1 Development of research tools

The introduction of genes for fluorescent proteins from other organisms into cells and animals in which they are not naturally present enables the visualisation of molecules and cells in real time. This gain-of-function research has advanced our knowledge of how biological systems work, for example, how insulin-producing beta cells are created in the pancreas of a growing embryo and mapping of individual nerve cells in the dense network in the brain.[44,45,46,47,48]

1.3.2 Gene transfer/targeting studies for development of new treatments

Gain-of-function research involving alteration of the expression of a gene of interest in cell culture or animal models to investigate gene function in normal or disease states has led to new knowledge in fields such as immunology and cancer, enabling the development of effective treatments.

CASE STUDY: The development of a new treatment for chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia is one of the most common types of leukaemia and affects around 1000 people in Australia every year.[49] Using gene transfer/gene targeting techniques, Australian researchers found, first in cell culture and then in an animal model, that a gene called *BCL-2* produced a particular protein (the BCL-2 protein) that promoted tumour development in chronic lymphocytic leukaemia and some other diseases.[50,51,52] As a result of this research, a new anti-cancer drug, venetoclax, that stops the action of the BCL-2 protein was able to be developed and was trialled in Australia and found to be safe and effective for treating chronic lymphocytic leukaemia.[53] In 2017, the Therapeutic Goods Administration (TGA) approved venetoclax for the treatment of chronic lymphocytic leukaemia and, in 2019, the Australian Government announced that it would be available through the Pharmaceutical Benefits Scheme.

1.3.3 Personalised medicine

Gain-of-function research has underpinned the genomics revolution, including developments in precision or personalised medicine, by determining the functional effects and clinical significance of a mutation and testing potential therapies.[54,55]

CASE STUDY: The search for a diagnosis and cure for Massimo Damiani[56,57]

At only one year old, Massimo was diagnosed with a leukodystrophy, a rare degenerative genetic condition in which the brain's ability to transmit signals to the body breaks down. Those with leukodystrophy have a life expectancy of months to several years. This condition is currently incurable. Massimo's specific type of leukodystrophy and thus any possible treatments were unable to be determined. Spurred by Massimo's parents, an Australian-led research team pioneered a new 'trio whole genome' sequencing approach, which revealed that Massimo's condition was caused by mutations in a gene called *DARS1*, which had not previously been associated with this disease. Melbourne researchers used gain-of-function research involving CRISPR gene editing to produce mice that have a new characteristic – the same type of disease as Massimo. These models can now be used to test potential treatments.

Tragically, Massimo passed away before he could benefit from the research conducted in his name. However, precision treatments, including stem cell and gene therapies, are in development with the aim of entering clinical trials. These treatments have the potential to help many thousands of other children around the world and could go on to help people with other neurodegenerative conditions – like multiple sclerosis that affects more than 25,000 Australians[58] and motor neuron disease that affects about 2,100 Australians at any one time.[59]

1.3.4 Development of gene therapies

Gain-of-function research is a crucial step in the development of several emerging, cutting-edge therapies being co-developed in Australia, including gene therapy and stem cell therapy, which are already yielding benefits for patients with previously untreatable diseases.[60,61,62]

CASE STUDY: CAR T-cell therapy

In Australia, about 370 people are diagnosed with acute lymphoblastic leukaemia each year. Of these, more than 200 are children under 15.[63] Australian researchers were involved in the clinical trials that demonstrated the safety and efficacy of a chimeric antigen receptor (CAR) T-cell therapy (Kymriah) in patients with relapsed or refractory paediatric acute lymphoblastic leukaemia where other treatments have failed. CAR T-cell therapies involve extracting a patient's own immune cells (T cells) and modifying them using a viral vector (a virus that has been modified so that it is unable to cause disease). The T cells are modified to contain a gene that enables the cells to express a receptor on their surface that recognises and directs the immune system to attack cancerous cells. The T cells expressing the new receptor are then expanded and reintroduced into the primed patient.[64,65] Kymriah was approved by the TGA in December 2018 and the Australian Government announced in 2019 that it would be the first publicly funded CAR T-cell therapy in Australia.

1.3.5 Vaccine development

Gain-of-function research has underpinned the generation of vaccines against viral and bacterial diseases that have significant negative impacts on human health.[8,10,66]

CASE STUDY: The development of the first vaccine against human papillomavirus

Gain-of-function research played a crucial role in the development of a vaccine against human papillomavirus (HPV), which can cause cervical and other cancers. The development of the HPV vaccine was based on the discovery that using recombinant DNA technology to express the capsid (coat) protein of the virus in yeast cells resulted in self-assembly into virus-like particles (VLPs). As these particles do not contain any viral genetic material, they are not infectious but elicit an immune response that protects the individual against infection if exposed to HPV.[67,68] Yeast cells with the gained function to produce VLPs are still used for commercial production of the vaccine. Since its inclusion in the National Immunisation Program in 2007, the HPV vaccine has already significantly decreased the incidence of high-grade cervical abnormalities in young women, with modelling showing that cervical cancer is now on track to be eliminated as a public health problem in Australia within the next 20 years.[69,70] In England, the HPV immunisation programme introduced in 2008 has almost eliminated cervical cancer in women born since 1 September 1995.[71]

1.3.6 Preclinical testing of vaccines and therapeutics

Gain-of-function research is often used to create animal models of viral disease to test the safety and efficacy of candidate vaccines and therapeutics prior to human trials. For example, mouse models of SARS-CoV-2 infection with a virus adapted to infect mice, or mouse cells modified to display the human receptor (ACE2) that the virus uses to infect human cells, were used to demonstrate the pre-clinical safety and efficacy of the Novavax and Moderna vaccines against SARS-CoV-2. Testing in such animal models is a crucial step before the commencement of clinical studies in humans.[72,73,74,75,76,77,78,79,80]

2. Concerns about some gain-of-function research

Gain-of-function research can be 'of concern' if it changes the characteristics of an infectious agent in a way that could increase the risk of harm to humans. Such research is generally performed to study a particular infectious agent and to develop strategies and technologies to prevent, detect or treat human infection by the agent.

Concerns about certain gain-of-function experiments have been heightened by speculation that the SARS-CoV-2 virus may have been created in a laboratory as the product of gain-of-function research. These concerns have prompted calls from some members of the Australian community to ban gain-of-function research, for example in a petition received by the Parliament of Australia and answered by the Minister for Health and Aged Care, in late 2021.[81]

Concerns about some gain-of-function experiments involving infectious agents can be broadly categorised into two areas. The first is biosafety where concerns focus on the risks of accidental release of a harmful infectious agent from containment; these concerns reflect the inherent risks of working with certain microorganisms, which may be increased if they are used in gain-of-function research. The second area is biosecurity where concerns focus on the risks that the results of the research could be deliberately misused (dual-use research of concern).

These concerns need to be assessed against the potential benefits of the research; for example, gain-of-function research may be required to understand the factors that lead to serious disease in humans and to develop therapeutics or vaccines to alleviate or prevent the disease.

As outlined in the terms of reference, this review is to report on any 'gain-of-function research that could increase the harmfulness of an infectious agent to humans'.[a] This section outlines the categorisation used in the review to identify this subset of gain-of-function research within the broader category of life sciences research, as well as providing further background on community concerns. It includes but is not limited to research involving enhanced pathogens with pandemic potential.

2.1 Categorisation of research

An infectious agent (also called a pathogen or germ) is a biological agent that causes disease or illness in its host. Most infectious agents are microorganisms (such as bacteria, viruses, fungi and protozoa), parasites and prions. However, not all microorganisms cause disease or illness – for example, 'good' bacteria present in the human body's normal flora.

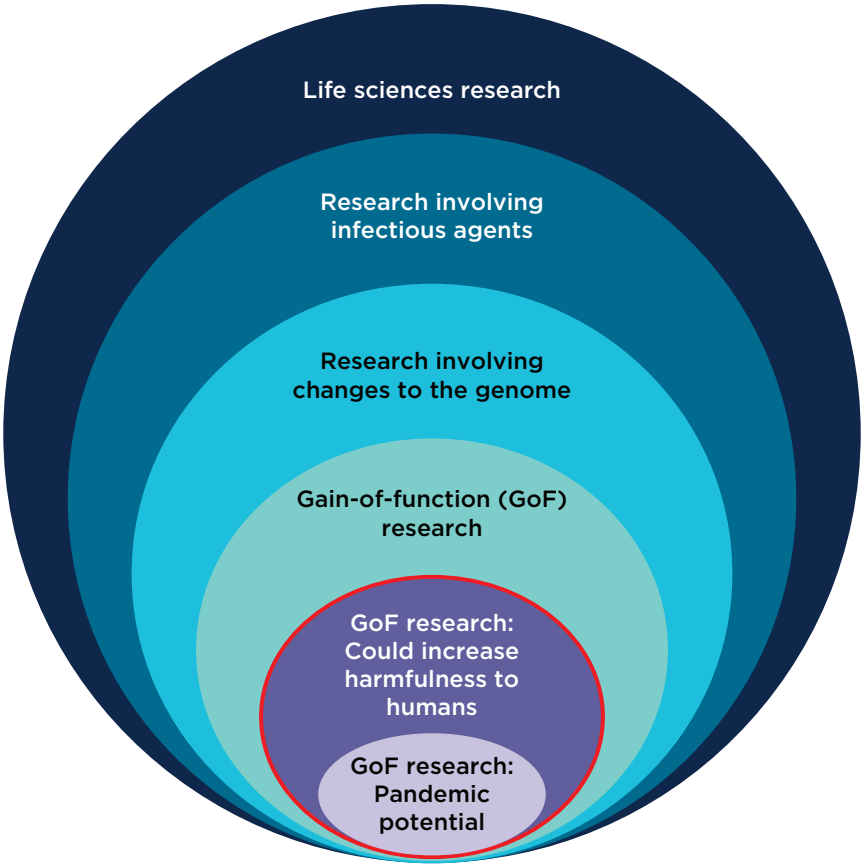
Research that involves infectious agents, and research that involves changes to the genome that lead to gain of function, are usually conducted in the field of life sciences – sciences concerned with living things such as biology, botany and physiology. As detailed in **Section 1.2.2** above, gain-of-function experiments are undertaken in many biological systems, of which only a fraction involve infectious agents and an even smaller proportion increase the pathogenicity or transmissibility of the infectious agent. Similarly, not all gain-of-function research involving infectious agents raises significant concerns or risk to human health.[8]

For the purposes of this report, life sciences research has been categorised according to whether it involves infectious agents, the degree to which gain-of-function research is involved, and the level of concern the research may entail, as outlined in **Figure 3**.

a For the purposes of this review, gain-of-function research that could increase the harmfulness of an infectious agent to humans is described as 'gain-of-function research of concern'.

This categorisation highlights how gain-of-function research that could increase the harmfulness of an infectious agent to humans fits within life sciences research. More information on the types of gain-of-function research that could increase harmfulness to human health, including research that could increase the 'pandemic potential' of an infectious agent, is provided in **Sections 2.1.1** and **2.1.2** below.

Figure 3. Categorisation of research



2.1.1 Gain-of-function research that could increase the harmfulness of an infectious agent

Gain-of-function research that could increase the harmfulness of an infectious agent to humans represents a subset of gain-of-function research, as highlighted in **Figure 3**. The following characteristics may be conferred on an infectious agent during the conduct of the research that may increase its harmfulness to humans:

- enhanced production of the infectious agent due to changes in its replication cycle or growth
- enhanced morbidity and mortality in relevant animal models
- enhanced transmissibility and host susceptibility in mammals (for example, altered host or tissue range, altered route of transmission, increased infectivity in an animal model)
- evasion of existing natural or induced immunity
- resistance to drugs or evasion of other medical countermeasures such as vaccines, therapeutics or diagnostics.[9,33]

An example of this type of gain-of-function research was the production of H5N1 influenza A viruses that are airborne-transmissible between ferrets, compared to the non-airborne transmissible natural version or 'wild type', raising the possibility that the virus strain may be transmissible to other mammals such as humans via the aerosol route.[8]

2.1.2 Gain-of-function research involving a pathogen with pandemic potential

Concerns about gain-of-function research have led to calls to ban such research, especially where it involves infectious agents with pandemic potential. An infectious agent with 'pandemic potential' is one that is highly transmissible and capable of wide and uncontrollable spread in human populations and highly virulent and likely to cause significant morbidity (illness) and/or mortality (death) in humans. An infectious agent with both these properties is also described internationally as a 'pathogen with pandemic potential' (PPP).[12]

Infectious agents that have the potential to cause human pandemics, or have caused a human pandemic, include: the H5N1 and H7N9 influenza viruses, also referred to as bird or avian influenzas; the SARS-CoV virus, which caused an epidemic in several countries in 2003; and the SARS-CoV-2 virus, responsible for COVID-19 disease.[5,7,9,22]

In a very small subset of gain-of-function research, characteristics may be conferred on an infectious agent that may increase its pandemic potential or cause it to acquire pandemic potential. In the USA, this has been called research involving 'enhanced potential pandemic pathogens' (enhanced PPP).

This review focused on identifying 'gain-of-function research that could increase the harmfulness of an infectious agent to humans', which is inclusive of but broader than creating enhanced PPP.

2.2 Risks of working with microorganisms

In life sciences research involving microorganisms, some research is associated with risks because of the characteristics of the microorganism and its ability to cause disease or illness (that is, an infectious agent). In a smaller number of cases, this type of research may involve techniques that lead to gain of function, and the risks may be increased because of the nature of the changes to the characteristics of the microorganism.

The Australian/New Zealand Standard *Safety in laboratories. Part 3: Microbiological safety and containment* (AS/NZS 2243.3:2010) (ANZ Standard) describes the classification of microorganisms that are infectious for humans and animals according to the degree of risk. This classification represents a modification of the World Health Organization (WHO) guidelines (2004) on the classification of microorganisms.[2] It is based on the pathogenicity of the microorganism, its mode of transmission and host range, the availability of effective preventive measures and the availability of effective treatment. Examples in the ANZ Standard of the risk level for microorganisms that are infectious for humans and animals are outlined in **Table 4**.[23,82]

Table 4. ANZ Standard: Examples of risk level of microorganisms that are infectious for humans and animals[23]

Risk level	Description	Examples
Risk Group 1 (low individual and community risk)	A microorganism that is unlikely to cause human or animal disease.	No examples provided in the ANZ Standard.
Risk Group 2 (moderate individual risk, limited community risk)	A microorganism that is unlikely to be a significant risk to laboratory workers, the community, livestock, or the environment; laboratory exposures may cause infection, but effective treatment and preventive measures are available, and the risk of spread is limited.	Bacteria: • *Clostridium* spp. • *Helicobacter pylori* • *Legionella* spp. • *Staphylococcus aureus* Viruses: • Adenovirus • Herpes Simplex virus • Murray Valley encephalitis virus • Hepatitis C virus
Risk Group 3 (high individual risk, limited to moderate community risk)	A microorganism that usually causes serious human or animal disease and may present a significant risk to laboratory workers. It could present a limited to moderate risk if spread in the community or the environment, but there are usually effective preventive measures or treatment available.	Bacteria: • *Chlamydia psittaci* • *Yersinia pestis* Viruses: • SARS coronavirus (from cultures and concentrates) • Human immunodeficiency virus • Influenza viruses (highly pathogenic strains)
Risk Group 4 (high individual and community risk)	A microorganism that usually produces life-threatening human or animal disease represents a significant risk to laboratory workers and may be readily transmissible from one individual to another. Effective treatment and preventive measures are not usually available.	No bacteria currently classified in Risk Group 4. Viruses: • Ebola virus • Hendra virus

The ANZ Standard also sets out requirements, responsibilities and general guidelines for the safe handling and containment of microorganisms and prions in laboratories (further information is provided in **Section C.2.1.**). The WHO *Laboratory Safety Manual* (2020) provides guidance about evidence-based and transparent assessment of the risks of working with microorganisms, to enable countries to implement economically feasible and sustainable laboratory biosafety and biosecurity policies and practices that are relevant to their individual circumstances and priorities. The risk assessment framework builds on previous classifications of microorganisms in terms of risk-hazard groups and biosafety/containment levels. It recognises, however, that the risk group of a microorganism may not directly correspond to the containment or biosafety level of a laboratory in which it should be handled. In addition, the actual risk of a given scenario is influenced not only by the microorganism being handled, but also by the procedure being performed and the training and competence of the laboratory personnel engaging in the laboratory activity.[2]

Certain microorganisms are also identified under the Security Sensitive Biological Agent (SSBA) Regulatory Scheme, if they have been assessed as posing a security concern to Australia. The List of SSBAs includes biological agents and toxins that may be used for a terrorist or criminal act and agents that could be developed, produced, stockpiled, acquired or retained in types and quantities that could allow the biological agent to be used as a weapon. Further information is provided in **Section C.2.2.1**.

2.3 Dual-use research of concern

The applications of research, knowledge and technologies may generate risks caused by accidents and by inadvertent or deliberate misapplications with the intention to cause harm. The possibility that research might be misused is a long-standing concern for the science community. The responsible conduct of research requires potential risks from inadvertent or deliberate misuse to be identified, mitigated and managed.[3,4,83,84]

Legitimate research that is intended to provide benefit, but could also inadvertently or deliberately be used to cause harm, has been described as 'dual-use research of concern'. It may refer to work in the life sciences; however, the principles are also applicable to other fields, including engineering and information technology. It encompasses everything from information to specific products of such research that have the potential to create negative consequences for health and safety, agriculture, the environment or national security.

In life sciences research, some research involving infectious agents may be of concern because of its potential for dual use. In a smaller number of cases, this type of research may involve techniques that lead to gain of function. Examples of such experiments that may be classified as dual-use research of concern include those that:

- could demonstrate how to:
  - render a vaccine ineffective
  - confer resistance to therapeutically useful antibiotics or antiviral agents
  - enhance the virulence of a pathogen or render a non-pathogen virulent
  - increase the transmissibility of a pathogen
  - alter the host range of a pathogen
  - enable the evasion of diagnosis and/or detection by established methods
  - enable the weaponisation of a biological agent or toxin
  - enable genetic sequencing of pathogens
  - synthesise pathogenic microorganisms
- involve any use of Variola virus (smallpox)
- attempt to recover/revive past pathogens.[85,86]

PART 2: Australian regulatory framework

Part 2 outlines the framework for regulation and oversight of life sciences research in Australia (**Section 3: Legislation and controls**). A comparison of this framework with those in other relevant countries is provided in **Part 4: International comparisons**.

The information presented in this part of the report is based on information sourced from Australian Government agencies that are responsible for the regulation and oversight of such biological research, as well as from international reports and academic literature.

Key points:

Australian regulatory framework

- Research in Australia is expected to be conducted responsibly and be ethically justified. Biosafety or biosecurity risks must be identified and effectively mitigated and the potential for inadvertent or deliberate misuse of the research must be minimised.
- Australia's framework for the regulation and oversight of research is comprehensive and aims to ensure the safe, responsible and ethical conduct of research. The framework includes a combination of Commonwealth and state/territory legislation, national standards and guidance, as well as local institutional governance and practices.
- Controls applied to all life sciences research also apply to research that involves infectious agents, including potential gain-of-function research. These controls include ethics and safety (including biosafety and biosecurity) approvals from government bodies and/or institutional committees that encompass consideration of the risks and benefits of the research.
- There are additional controls for, and oversight of, research involving infectious agents and/or research involving changes to the genome including Commonwealth and state and territory legislation biosecurity and gene technology legislation.
- Relevant approvals must be obtained before research commences. Monitoring and reporting requirements ensure that research is conducted in accordance with relevant licences and approvals. Monitoring and reporting also ensure that any issues that arise during the conduct of the research are detected and adequately addressed.

3. Legislation and controls

The framework in Australia for the regulation and oversight of life sciences (sciences concerned with living things such as biology, botany and physiology) also applies to research that involves infectious agents and research that leads to gain of function. The framework includes a combination of legislation, policies, standards and guidance, as well as local institutional governance and practices. It seeks to ensure:

- the quality and significance of the research
- that the benefits of the research are clear and tangible
- that the objectives of the research cannot be delivered by another means
- that ethics and safety (including biosafety and biosecurity) approvals are obtained from government bodies and/or institutional committees that encompass consideration of the risks and benefits of the research, with approvals obtained before commencement of the research.

Information about the framework for the regulation and oversight of research in Australia is provided as follows:

- **Section 3.1**: Application of the framework as determined by the elements of the research
- **Section 3.2**: Application of the framework during the research cycle
- **Section 3.3**: A case study to illustrate how the framework is applied.

3.1 Elements of the research

The application of the framework for regulation and oversight of research in Australia is determined by the specific elements of the research, and is summarised in **Figure 4** and **Table 5**. Detailed information is provided in **Appendix C**.

Figure 4. Summary: Legislation and controls governing life sciences research

The controls applying to each classification of life sciences research also apply to the other classifications of research that they encompass.

Box 1: Applies to life sciences research

- Australian Code for the Responsible Conduct of Research
- Animal use: Animal welfare legislation (state, territory); *Environment Protection and Biodiversity Conservation Act 1999*; Australian code for the care and use of animals for scientific purposes
- Human research (including biospecimens): National Statement on Ethical Conduct in Human Research; state/territory human tissue legislation
- Work health and safety
- Controlled goods and technology:
  - *Customs Act 1901*
  - Customs (Prohibited Exports) Regulations 1958
  - *Defence Trade Controls Act 2012*
  - Defence Trade Control Regulations 2013
  - Defence and Strategic Goods List (DSGL) 2021
  - *Weapons of Mass Destruction (Prevention of Proliferation) Act 1995*
- *Therapeutic Goods Act 1989*
- Funding agencies: Contracts and policies
- Institutional governance and practices

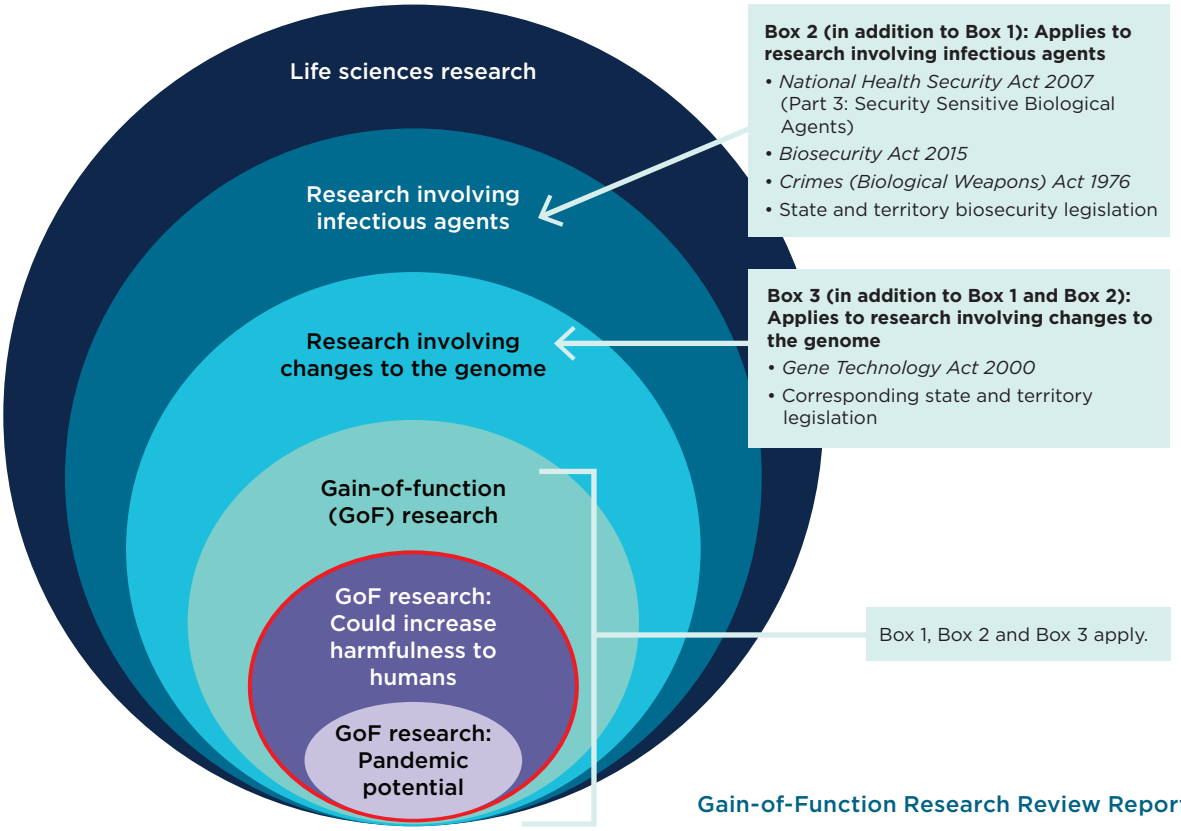


Table 5. Summary: Legislation and controls governing life sciences research

Elements	Legislative controls		Additional external controls	Institutional controls
	Act/Regulation	Responsible Agency		
Work health and safety (including safety for the use of infectious agents) (See **Sections C.1.1** and **C.2.1**)	*Work Health and Safety Act 2011(Cth)*[b] Work Health and Safety Regulations 2011 (Cth)	Attorney General's Department Comcare Safe Work Australia	WHS also covers biological hazards – organic substances that pose a threat to the health of humans and other living organisms. Australian/New Zealand Standard *Safety in Laboratories. Part 3: Microbiological safety and containment* (AS/NZS 2243.3:2010)	Institutional work health and safety (WHS) committee or biosafety committee (IBC)
	Work health and safety (WHS) legislation in each jurisdiction	State and territory WHS regulators		
Use of animals (See **Section C.1.2**)	State and territory legislation for animal welfare/animal research	State and territory animal welfare departments	Australian code for the care and use of animals for scientific purposes, 2013 (updated 2021), which is incorporated in all state and territory legislation.	Animal Ethics Committee (AEC)
	Environment Protection and Biodiversity Conservation Act 1999 (Cth)	Department of Agriculture, Water and the Environment		
Human research including use of human tissues or cells (See **Section C.1.3**)	*Research Involving Human Embryos Act 2002 (Cth)* and corresponding state and territory legislation	Licensing of research involving human embryos by Embryo Research Licensing Committee	• National Statement on Ethical Conduct in Human Research, 2007 (updated 2018) • Ethical guidelines on the use of assisted reproductive technology in clinical practice and research, 2017	Human Research Ethics Committee (HREC)
	State and territory human tissue legislation	State and territory government departments		

b Cth = Commonwealth

Elements	Legislative controls		Additional external controls	Institutional controls
	Act/Regulation	Responsible Agency		
Controlled goods and technology (See **Section C.1.4**)	*Customs Act 1901* and Customs (Prohibited Exports) Regulations 1958 (Cth)	Department of Immigration and Border Protection Department of Defence	Defence and Strategic Goods List (DSGL) 2021	Institutional work health and safety committee or biosafety committee
	Defence Trade Controls Act 2012 (Cth) and associated regulations	Department of Defence		
	Weapons of Mass Destruction (Prevention of Proliferation) Act 1995 (Cth) and associated regulations	Department of Defence		
Therapeutic Goods (See **Section C.1.5**)	*Therapeutic Goods Act 1989 (Cth)* and associated regulations	Department of Health	N/A	Human Research Ethics Committee
Infectious agents (See **Section C.2**) (biosecurity)	*National Health Security Act 2007 (Cth)* (Part 3): Part 3 - Regulation of Security Sensitive Biological Agents (SSBAs) National Health Security Regulations 2018	Department of Health	SSBA Standards Australian/New Zealand Standard *Safety in Laboratories. Part 3: Microbiological safety and containment* (AS/NZS 2243.3:2010)	Institutional work health and safety committee or biosafety committee
	*Crimes (Biological Weapons) Act 1976 (Cth)*and Crimes (Biological Weapons) Regulations 1980 (Cth)	Attorney-General's Department		
	Biosecurity Act 2015 (Cth) and associated regulations and legislative instruments	Department of Health: aspects of the Act related to human biosecurity Department of Agriculture, Water and the Environment: aspects of the Act related to environment, animal and plant biosecurity		
	Environment Protection and Biodiversity Conservation Act, 1999	Department of Agriculture, Water and the Environment		
	State and territory biosecurity legislation	State and territory regulators		

Elements	Legislative controls		Additional external controls	Institutional controls
	Act/Regulation	Responsible Agency		
Gene technology (See **Section C.3**)	*Gene Technology Act 2000 (Cth)*, Gene Technology Regulations 2001 (Cth) and corresponding state and territory legislation	Department of Health, Office of the Gene Technology Regulator Administered by: independent statutory office holder, the Gene Technology Regulator	N/A	Institutional Biosafety Committee
Laboratories and facilities: physical containment/ biosafety (See **Section C.4.2**)	<u>Infectious agents:</u> *National Health Security Act 2007 (Cth):* Part 3 - Regulation of Security Sensitive Biological Agents (SSBAs) and associated regulations: National Health Security Regulations 2018 SSBAs *Biosecurity Act 2015 (Cth)* and associated regulations: Approved arrangements <u>Genetically modified organisms (GMOs):</u> *Gene Technology Act 2000 (Cth)*, Gene Technology Regulations 2001 (Cth) and corresponding state and territory legislation	<u>Infectious agents:</u> Department of Health, Office of Health Protection and Response Department of Agriculture, Water and the Environment <u>GMOs:</u> Administered by: independent statutory office holder, the Gene Technology Regulator	SSBA Standards Australian/New Zealand Standard *Safety in laboratories. Part 3: Microbiological safety and containment* (AS/NZS 2243.3:2010)	Institutional work health and safety committee or biosafety committee
Animal facilities: Licensing (See **Section C.4.1**)	State and territory legislation	State and territory animal welfare departments	Australian code for the care and use of animals for scientific purposes, 2013 (updated 2021) is incorporated in all state and territory legislation	N/A

Elements	Legislative controls		Additional external controls	Institutional controls
	Act/Regulation	Responsible Agency		
Funding agencies (See **Section C.1.6**)	Legislation relevant to funding contracts	Individual funding agency	Peer review (funding applications) Funding contracts Australian Code for the Responsible Conduct of Research Policies, standards and guidelines	Institutional policies and practices
Training and competence (See **Section C.1.9**)	Training requirements under relevant legislation (e.g. as applies to work health and safety, animal research, human research, gene technology, handling and use of microorganisms including SSBAs, controlled goods and technology, biosafety and biosecurity)	Agencies responsible for relevant legislation	International, national and professional policies, guidelines and standards	Relevant institutional committees Institutional policies and practices

3.2 The research cycle

This section summarises how the regulation and oversight of research is applied during the various stages of the research cycle.

3.2.1 Development

When developing a research proposal, the researcher must ensure that all requirements under relevant legislation, policies, standards and guidelines are met, that ethical issues are addressed, and that biosafety and biosecurity risks are identified and mitigated.

3.2.2 Funding

Research proposals outlined in funding applications are subject to peer review so that only those projects that are determined to be significant and high quality, with potential to have high impact on the research field(s) involved, are funded.

3.2.3 Prior to commencement

Before the research commences, all controls relevant to the nature of the research must be in place, as outlined in **Table 5**. The institution must be appropriately licensed (e.g. research involving use of animals or GMOs); the researchers must be appropriately licensed and trained and competent; facilities where the work will be conducted must be appropriately licensed for biosafety and, where necessary, animal welfare; and relevant ethics and safety (including biosafety and biosecurity) approvals must be obtained from institutional committee(s) (e.g. AEC, HREC, IBC, WHS) and state/territory and Commonwealth departments and agencies.

Prior approval must be obtained from relevant Commonwealth departments before importation of animals or materials (e.g. biological agents, cell cultures, biospecimens) to be used in the research, as outlined in **Table 5**.

Funding agencies require approvals for ethics and safety to be in place before work commences and compliance of funded research with all relevant legislation, policies, standards and guidelines.

The aim of these controls is to ensure that the proposed research is responsible and ethically justified, the benefits and potential risks of the proposed research are assessed, potential risks are effectively mitigated and the potential for inadvertent or deliberate misuse of the research is minimised. At any stage during these processes, the proposed research may be modified in order to address any issues raised.

3.2.4 Monitoring and reporting

Where relevant, the research, the researchers' work and the facility where the work is conducted are monitored or inspected by institutional ethics and safety committees as well as state/territory and Commonwealth departments and agencies. Monitoring includes, for example, that conducted by the OGTR (GMOs), Department of Health (SSBAs), Department of Agriculture, Water and the Environment (imported goods), and Department of Defence (controlled goods, technologies and services). In addition, the institution responsible for the research is subject to monitoring and compliance checks by state/territory and Commonwealth departments and agencies and funding agencies.

Institutions and researchers are also required to report regularly (e.g. annually) or as required by particular circumstances (e.g. following adverse events) to institutional committees, state/territory and Commonwealth departments and agencies and funding agencies.

The aim of these controls is to ensure the research is conducted responsibly, ethically and with integrity and in compliance with relevant legislation, and in accordance with the approvals from institutional committees and state/territory and Commonwealth departments, and the requirements of funding agencies. In addition, these controls seek to ensure that any issues that arise during the conduct of the research are detected and are adequately addressed.

3.2.5 Completion and dissemination of outcomes

At the end of the research, researchers must provide final reports to institutional committees and funding agencies as required. Dissemination of research outcomes must be in accordance with relevant policies, guidelines and standards (e.g. requirements under the Australian Code for the Responsible Conduct of Research, open access policies of funding agencies).

In addition, prior to dissemination of the research outcomes, researchers must obtain approval, if required, from the Department of Defence (controlled goods, technologies and services), e.g. for the electronic supply, publication and the brokering of goods and technology arising from that research.

The aim of these controls is to ensure that the outcomes of research are disseminated openly, responsibly and accurately, with disclosure and management of conflicts of interests, and minimisation of the potential for misuse of the research outcomes.

3.3 Case study

A hypothetical case study is presented below to illustrate how the frameworks for regulation and oversight of research in Australia are applied for gain-of-function research to proceed. The controls applicable to this case study are outlined in **Figure 5**.

The research involves the use of a genetically modified bacterium in an animal model. The aim of the study is to investigate (1) the mechanisms of transmissibility of the bacterium by examining the effect of the genetic modification on its transmissibility and (2) whether the transmissibility of the bacterium can be reduced or abolished with a new treatment.

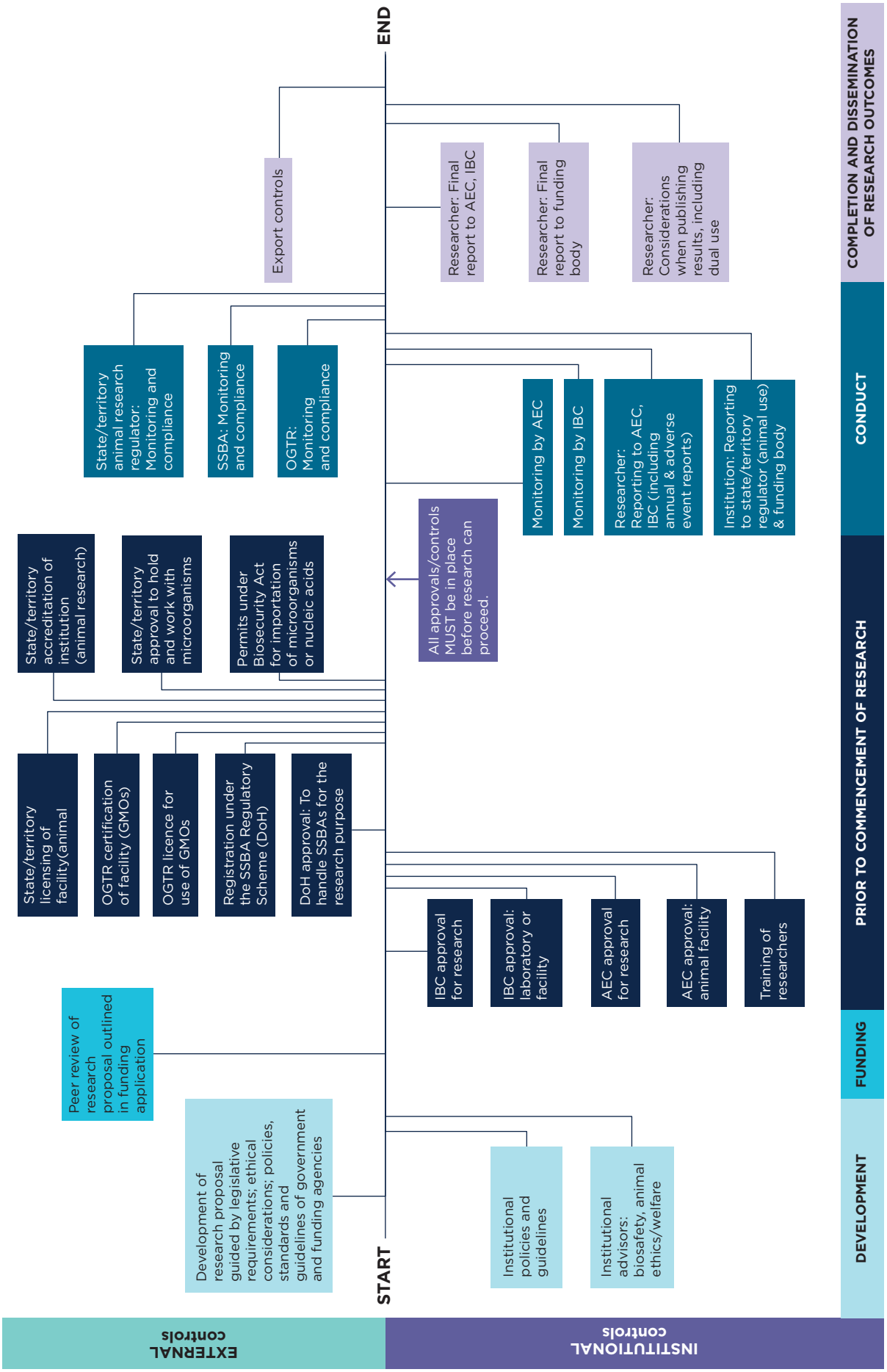
The classification of the bacterium used in the research is as follows:

- Australian/New Zealand Standard *Safety in laboratories. Part 3: Microbiological safety and containment* (AS/NZS 2243.3:2010) (ANZ Standard): Risk Group 3 – high individual risk, limited to moderate community risk
- Security Sensitive Biological Agents List: Tier 2 – biological agents of high security concern
- Defence Strategic Goods List: 1C351 – human pathogens, zoonoses and 'toxins'.

The proposed genetic modification to the bacterium requires a licence from the OGTR.

A PC3 facility is required for the handling of the bacterium under the ANZ Standard.

Figure 5. Case study: Controls for research project involving genetically modified SSBA Tier 2 bacteria in an animal model



PART 3: Relevant research

Part 3 outlines the methodology (**Section 4: Methodology**) used to identify 'any gain-of-function research that could increase the harmfulness of an infectious agent to humans that has been funded or conducted by the Australian Government or its agencies over the last 10 years', as per the terms of reference for the review (refer to **Appendix A**).

Part 3 also outlines the results of the review – that is, identification of the volume and nature of gain-of-function research, over the last 10 years, that could have increased the harmfulness of an infectious agent to humans (**Section 5: Results**). **Section 5.2.3** includes information about the controls that were in place, both before the research proceeded and during the conduct of the research, consistent with the Australian regulatory framework described in **Part 2**.

Key points:

Methodology

- The review sought to identify any gain-of-function research that could increase the harmfulness of an infectious agent to humans that has been funded or conducted by the Australian Government or its agencies over the last 10 years.
- The review methodology was designed to be robust, to ensure a consistent approach and to minimise bias. All infectious diseases projects (excluding research in plants) funded or conducted by the Australian Government over the last 10 years were subject to consistent assessment and decision-making by an Expert Panel, with conflicts of interests managed appropriately (including for staff and observers such as NHMRC's CEO).

Results

Gain-of-function research that could increase the harmfulness of an infectious agent

- Over the last 10 years, the Australian Government has funded or conducted 17 research projects that were identified in this review as gain-of-function research that could increase the harmfulness of an infectious agent to humans.[c]
- These projects comprise less than 0.3% of the more than 6000 research projects involving infectious agents that were funded or conducted by the Australian Government in the same period.
- The 17 research projects identified were funded by NHMRC (10) and conducted by CSIRO (8); one was both funded by NHMRC and conducted by CSIRO. No other Australian Government agency was found to have funded or conducted gain-of-function research of concern over the last 10 years.
- This report does not identify individual researchers or institutions associated with gain-of-function research of concern. This approach is necessary to protect researchers from potentially serious threats to their personal and professional lives, as has been experienced by scientists around the world in the context of COVID-19.
- 13 research projects involved virological studies and 4 research projects involved bacteriological studies.
- The research projects aimed to achieve benefits for human health including better understanding of bacterial and viral infections and how to detect, prevent and treat these infections.
- All 17 research projects identified had in place the required approvals, licences or other controls (e.g. conducted in appropriate facilities) for the safe and ethical conduct of research, in accordance with Australia's regulatory framework.
- The research projects were monitored appropriately and there were no reported incidents involving infectious agents or GMOs during the conduct of any of the research projects.

c For the purposes of this review, gain-of-function research that could increase the harmfulness of an infectious agent to humans is described as 'gain-of-function research of concern'.

4. Methodology

This section outlines the methodology used to identify research that was in scope for the review.

The scope of the review was limited to that outlined in the terms of reference (**Appendix A**) – that is, any gain-of-function research that could increase the harmfulness of an infectious agent to humans and had been funded or conducted by the Australian Government or its agencies over the last 10 years. Depending on the context, this type of research is also described in this report as 'in scope', 'relevant research' and 'gain-of-function research of concern'.

Research that was not funded or conducted by the Australian Government or its agencies over the last 10 years was out of scope for the review. This included research funded or conducted solely by an overseas funding agency, a state or territory government or a private organisation. It is important to note that all research conducted in Australia regardless of its funding source, and regardless of the organisation or individual conducting the research, is subject to Australia's framework for the regulation and oversight of research as described in **Part 2**.

4.1 Overview

Because 'gain of function' is not a standard term used to describe research, it could not be used as a search term for the large amount of research funded or conducted by the Australian Government or its agencies over the last 10 years. Therefore, the review needed to start by identifying a broader range of research projects and then to assess those projects consistently to identify any relevant gain-of-function research.

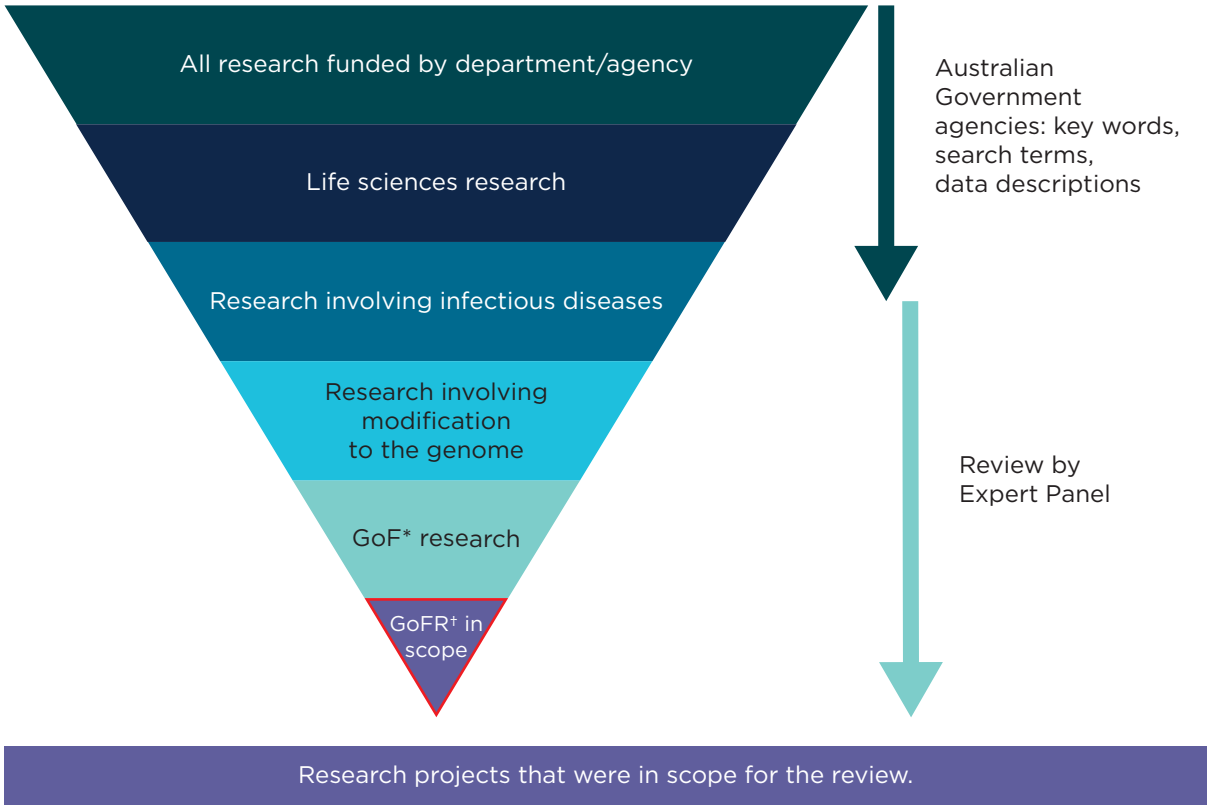
To do this, the review used the categorisation outlined in **Section 2.1**, starting with life sciences research involving infectious diseases.

The process for identification of research projects that were in scope was designed to be robust, to ensure a consistent approach and to minimise bias. In brief, the process involved:

- identification by relevant agencies of projects that *may be* in scope for the review (that is, all research involving infectious diseases in humans or animals; refer to the inclusion and exclusion criteria defined in **Section 4.2** below for more information)
- review of information about these projects by an Expert Panel to identify those that *were* in scope for the review (that is, gain-of-function research that could increase the harmfulness of an infectious agent to humans that had been funded or conducted by the Australian Government or its agencies over the last 10 years).

The process is summarised in **Figure 6** and in **Table 6**, with further details provided in **Appendix D**.

Figure 6. Identification of research projects that were in scope



** GoF: gain of function*

† GoFR: Gain-of-function research

Table 6. Key elements: Methodology for identification of research projects that were in scope

Element	Details
Establishment of an Expert Panel	Individuals from government agencies with expertise relevant to infectious diseases and gain-of-function research were invited to be members of this panel (see **Section D.1**). The process of establishing the Expert Panel and review of relevant research projects included ongoing disclosure of interests and management of any conflicts of interest (see **Section D.1.3**).
Identification of research projects that were in scope	This process involved: 1. identification of research projects that *may be* in scope by all relevant Australian government agencies 2. review of information about identified research projects to determine those that *were* in scope by the Expert Panel. (See **Sections 4.2** and **4.3** and **Appendix D**) Further information on steps 1 and 2 is presented below.
1. Identification of research projects that *may* be in scope	All relevant Australian Government agencies identified research projects that *may be* in scope, based on the inclusion and exclusion criteria (see **Section 4.2**).
2. Identification of research projects that *were* in scope	The Expert Panel reviewed information about research projects provided by relevant Australian Government agencies (see **Section 4.3**). This process comprised: • three phases: initial review, detailed review and agreement on categorisation • use of agreed criteria to enable consistent categorisation of research projects • regular meetings of the Expert Panel to review progress and discuss any issues that arose.

4.2 Identifying relevant infectious disease research projects

All Australian Government agencies that may have funded or conducted relevant research were asked to identify research projects that *may* be in scope for the review based on inclusion and exclusion criteria developed in consultation with the Expert Panel.

4.2.1 Inclusion criteria

Research projects that met all of the following criteria fulfilled the requirements under the terms of reference for the review and required review by the Expert Panel:

- funded or conducted by the Australian Government or its agencies, including where all or part of the project was conducted in another country
- relevant to infectious disease (excluding research in plants)
- active between 1 January 2010 and 15 September 2021 (which was the date of the first meeting of the Expert Panel).

Because 'gain of function' is not a standard key-word term used in applications for funding or research publications, it could not be used as a search term or an inclusion criterion.

4.2.2 Exclusion criteria

The following types of projects and grants did not meet the requirements under the terms of reference for the review and were excluded:

- Research projects that were not relevant to infectious disease such as cancer research or genetics research. It is possible that some of these projects involved gain of function. However, as they did not involve an infectious agent and/or infectious disease, they were out of scope.
- Research projects that involved plants or infectious agents of plants.
- Projects that involved surveillance, monitoring or diagnostic activities, including activities that involved laboratory work but did not involve experimental manipulation.
- Projects that that did not involve research. Examples included operational funding or funding for maintenance of a facility or laboratory including related salary costs, equipment and computer software; and procured health services such as screening for a particular condition.
- Block grant funding to institutions.
- Research projects where funding was offered but the project (and funding) did not proceed.

4.3 Decision making by the Expert Panel

Information about research projects provided by relevant Australian Government agencies was reviewed by the Expert Panel to identify projects that were in scope for the review. This process is described in detail in **Appendix D**.

The Expert Panel members categorised each project according to criteria that were based on characteristics of an infectious agent which may increase its harmfulness to humans (see **Section 2.1.1**). These criteria were developed in consultation with the Expert Panel to enable consistent decision making by members (**Appendix E**).

For projects where at least one member categorised the research as being potentially in scope, the project was discussed by the whole Expert Panel. The aim of this approach was to enable the decision about whether or not a project was in scope to be made collectively by the Expert Panel.

Prior to commencement of any discussion about a project, disclosure of interests and management of any conflicts of interest was undertaken in accordance with the requirements of the NHMRC's *Policy on the disclosure of interest requirements for prospective and appointed NHMRC committee members* (see **Section D.1.3**).[87] This ensured that Expert Panel members, observers and other NHMRC staff (including NHMRC's CEO) were not involved in discussions or decisions about a research project with which they had any interest or involvement.

A decision about the categorisation of the project was made by consensus. If a consensus decision could not be reached, the decision was deferred to the next meeting, which allowed members to review their positions. If following further discussion a consensus could not be reached, the Expert Panel reached a majority decision following a vote.

In reaching its decision about a particular project, the Expert Panel's discussions focused on the *potential* for the research to increase the harmfulness of an infectious agent to humans, as required by the terms of reference for the review. These discussions included the possibility that the research could increase the pandemic potential of an infectious agent that is already highly pathogenic in humans or cause it to acquire pandemic potential. Research that *could* increase the harmfulness of an infectious agent to humans (including but not limited to having pandemic potential), based on the research proposal, was identified as being in scope for the review. However, the identification of research as being in scope did not necessarily mean that the research *would* increase the harmfulness of an infectious agent to humans. Key decision points that informed these discussions are outlined in **Table 7**.

Table 7. Expert Panel: Key decision points

Type of research	Examples
No intent, and low likelihood, of creating something that is harmful to humans. This type of research was not of concern and was not in scope for the review.	• Knocking out a gene (loss of function) and then analysing function. • Creation of a library of mutants of an infectious agent and looking at effect of the mutations, but with no intention of selecting the mutant on the basis of increased virulence or transmissibility and therefore unlikely to create a microorganism that is harmful to humans. • Experimental conditions that are not designed to lead to gain of function, for example, testing of various concentrations of antibiotics. • Selecting mutants that have reduced survival compared to normal (wild type) and creating similar mutants. • Experiment conducted in an animal model with no chance of infecting humans. • Studies involving infectious agents with a low-risk route for transmission, for example, via mosquitoes compared to air-borne transmission.
Involving characteristics that already exist in nature. This type of research was not of concern and was not in scope for the review.	• Creating an infectious agent with a characteristic that already exists in nature (including level of virulence/transmissibility; e.g. an infectious agent that was already highly virulent and/or highly transmissible). • Trying to understand how mutants are created in nature (e.g. examining random transfers of elements between bacterial strains). • Regaining a previous function (e.g. previous resistance to a treatment). • Potential for creating a strain of an infectious agent that is resistant to treatments such as anti-viral drugs or antibiotics. However, a strain already exists that is resistant to the treatment.
Potential for creating something that may harm humans. This type of research was of concern and was in scope for the review.	• Creating a new species of an infectious agent that is more harmful than the original species. • Creating a new species of an infectious agent that is harder to treat than the original species. • Creating a new species of an infectious agent (or modification to an existing infectious agent) that, if released, would do harm. • Creating a chimera (an infectious agent that contains genetic material derived from two or more distinct infectious agents) with increased potential to harm humans (for example, increased virulence or transmissibility).

5. Results: Relevant gain-of-function research

This section provides information about research that was identified as being in scope for review – that is, gain-of-function research that could increase the harmfulness of an infectious agent to humans that had been funded or conducted by the Australian Government or its agencies over the last 10 years. It also describes the controls that were in place before this research proceeded and during the conduct of the research.

The information presented in this part of the report is based on information provided by relevant Australian Government agencies that may have funded or conducted relevant research, and using the methodology outlined in **Section 4** and **Appendix D**.

5.1 Research projects in scope

Australian Government agencies provided information about 6275 research projects that met the inclusion criteria as outlined in **Section 4.2.1** and thus *may* have been in scope. The number of projects identified by each Government agency is provided in **Table 8**.

These 6275 projects in infectious diseases were then reviewed by the Expert Panel to identify those that, based on the original research proposal, involved gain-of-function research that could increase the harmfulness of an infectious agent to humans and thus were in scope. As outlined in **Table 9**, the Expert Panel identified 20 projects as being in scope. Subsequent evaluation determined that of these, two projects were duplicate or linked projects and one project did not proceed, leaving 17 projects that remained in scope.

Further information on the process of review and decision making by the Expert Panel to arrive at this list of 'in scope' projects is provided in **Section 4.3** and **Appendix D**.

Table 8. Number of research projects identified that may have been in scope[d]

Portfolio	Agency	Number
Agriculture, Water and the Environment	Department of Agriculture, Water and the Environment	75
Defence	Department of Defence	9
Education, Skills and Employment	Australian Research Council	2357
Foreign Affairs and Trade	Department of Foreign Affairs and Trade	14
	Australian Centre for International Agricultural Research	9
Health	National Health and Medical Research Council (NHMRC)	3018
	Department of Health[e]	208
Industry, Science, Energy and Resources	Commonwealth Scientific and Industrial Research Organisation (CSIRO)[f]	547
	Department of Industry, Science, Energy and Resources	38
Total		**6275**

d The total number may include duplicate projects that were funded by more than one agency and hence identified by more than one agency. Projects were identified from grant funding data and other sources based on common key words and consistent with the inclusion criteria outlined in Section 4.2.1. Where programs of research (e.g. Cooperative Research Centres) were funded as a single grant, they are identified as one 'project'.

e Includes projects identified by the Health and Medical Research Office (Medical Research Future Fund); Office of Health Protection and Response; and the Population Health Division in the Primary and Community Care Group.

f CSIRO identified all relevant research conducted by CSIRO irrespective of funding source.

Table 9 outlines the number of research projects identified through this review. In summary:

- Over the last 10 years, the Australian Government has funded or conducted 17 research projects that were identified in this review as involving gain-of-function research that could increase the harmfulness of an infectious agent to humans.
- The projects comprise less than 0.3% of the total number of research projects involving infectious agents that were funded or conducted by the Australian Government in the same period.
- Of the 17 research projects identified, 10 were funded by NHMRC and 8 were conducted by CSIRO; one project was both funded by NHMRC and conducted by CSIRO. No other Government agency was found to have funded or conducted gain-of-function research of concern over the last 10 years.

Table 9. Number of research projects identified through the review

Phase	Number
Projects identified by relevant Australian Government agencies that *may* be in scope and were then reviewed by the Expert Panel	6275
Projects identified by the Expert Panel as being *in scope* (see methodology outlined in **Section 4.3** and **Appendix D**)	20
Duplicate/linked projects (n=2) and projects that did not proceed (n=1)	3
Projects that were in scope[g]	
Final projects that were in scope – all of which were funded by NHMRC or conducted by CSIRO or both	17
Percentage of total number of projects reviewed by the Expert Panel	0.27%

5.2 Information about relevant research

Information about these gain-of-function research projects is presented below in general terms and, where appropriate, aggregated form. This report does not identify individual researchers or non-Government institutions associated with relevant gain-of-function research. This approach is necessary to protect researchers from serious threats to their personal and professional lives, as has been experienced by scientists around the world in the context of research on COVID-19. In Australia, trolling, bullying and harassment of scientists, including death threats and/or threats of physical or sexual violence, have been reported by scientists after speaking to the media about COVID-19.[88]

5.2.1 Types of research

Of the research projects identified:

- 13 projects involved virological studies (Cedar virus, Ebola virus, filovirus, flavivirus, Hendra virus, influenza viruses including influenza A, lyssa viruses, Marburg virus, Nipah virus, rabies virus, SARS-like coronavirus, West Nile virus).
- Four projects involved bacteriological studies (*Escherichia coli, Mycobacterium ulcerans*, *Streptococcus pyogenes*, *Yersinia pestis*).
- 13 projects involved the use of live animals (mouse, ferret), while some other projects involved the use of animal tissue/cell lines (e.g. bat tissue, avian cells) and three projects involved the use of human tissues.
- Four projects did not involve the use of either an animal model or human tissues.
- 13 projects involved the use of GMOs in Australia and one project involved the use of GMOs in other countries (Canada, USA).

g Also described as 'gain-of-function research that could increase the harmfulness of an infectious agent to humans' or 'gain-of-function research of concern'.

5.2.2 Timeframes of the research

The terms of reference required the review to identify any gain-of-function research that could increase the harmfulness of an infectious agent to humans over the last 10 years. This was operationalised as a period just over 10 years and the inclusion criterion (**Section 4.2.1**) for the review was any relevant research project that was active between 1 January 2010 and 15 September 2021 (which was the date of the first meeting of the Expert Panel).

Accordingly, the start and end date of these 17 projects varied over the last 10 years, with some having commenced before, but still active on, 1 January 2010 and others starting and ending within the period investigated. Most of the projects had ended as at 15 September 2021, with only one of the projects still active as at 28 January 2022.

5.2.3 Anticipated benefits and outcomes of the research

The anticipated benefits of the research projects identified by the review, based on the new knowledge that they would generate, are summarised below. As outlined in **Section 4.3**, the identification of projects that were in scope was based on the Expert Panel's assessment of whether the research *could* increase the harmfulness of an infectious agent to humans. The identification of a project as being in scope did not necessarily mean that the project *would* increase the harmfulness of an infectious agent to humans. Indeed, **Section 5.3** below outlines the controls that were in place for this research, including biosafety and biosecurity controls, to ensure that the research was conducted safely and monitored appropriately.

The anticipated benefits and outcomes below are primarily based on the original research proposals as submitted, noting that some research may not have proceeded exactly as outlined in the original proposal. To minimise the potential for identification of researchers and institutions involved with the projects, information about the projects is presented in general terms and, where appropriate, aggregated form.

The anticipated benefits and outcomes included:

- Forecasting and preparing for a 'bad' flu season, and potentially developing new drugs that inhibit severe flu, by identifying the features of influenza viruses that predict virulence.
- Determining the vulnerability of a species (including birds and humans) to 'bird flu' outbreaks by advancing understanding of the natural evolution of an avian influenza virus from a low pathogenic virus to a highly pathogenic variant.
- Improving the ability to detect swine-origin influenza strains of concern (to pigs and to humans) by identifying the molecular and genetic basis for pathogenicity of swine-origin influenza.
- Enabling the rapid identification and response to flaviviruses in Australia (flaviviruses are mosquito-borne viruses that can cause large disease outbreaks, such as Dengue virus, West Nile virus, yellow fever virus and Japanese encephalitis virus) by advancing understanding about the viral factors that determine the transmission and virulence of flaviviruses.
- Determining vaccine protection against lyssaviruses (including the Australian bat lyssavirus (flying fox variant) that can be transmitted from bats to humans, causing serious illness) by creating a laboratory animal model (mouse) to study lyssaviruses more readily.
- Potentially developing vaccines and therapeutics to filoviruses and henipaviruses (for example, Cedar virus, Ebola virus, Hendra virus, Marburg virus and Nipah virus) by identifying the viral factors that determine the virulence and pathogenicity of these viruses.
- Assessing the potential threat of bat viruses to human health by investigating the mechanisms of cross-species transmission of potential zoonotic viruses carried by bats.[h]
- Advancing understanding of how pandemics happen by determining the origin and evolution of a bacterial pathogen involved in an historical pandemic, including understanding the mutations that contributed to its increased virulence.

h This research originally proposed to investigate the potential threat of SARS-like coronavirus, which is found in bats and is genetically closely related to the virus that caused the 2003 SARS outbreak in humans, but the research ended up focusing on, and identifying, other viruses (not coronaviruses) that had not previously been identified in bats.

- Enabling the detection of disease-causing bacteria and the development of better treatments and vaccines by identifying how various bacteria make toxins, cause disease and develop resistance to antibiotics.

So, while gain-of-function research may create an infectious agent that *could* cause harm to humans – such as a virus or bacterium that is more transmissible, virulent or pathogenic – this research was carried out because it is vitally important to prepare for, detect, treat and where possible prevent serious outbreaks of disease in humans.

5.3 Conduct of the research and controls in place

Of the 17 research projects identified, all were conducted at appropriate research sites such as universities or CSIRO research sites. For one project, the components of the project involving live infectious agents/genetically modified organisms (GMO) were conducted abroad (Canada, USA).

As part of the review process, further information on each project was obtained from the institution responsible for the project (the administering institution). This included evidence that all controls as required under Australia's regulatory framework for the type of research involved were in place during the conduct of the research. These controls included, but were not limited to:

- Approval from the Institutional Biosafety Committee (IBC). The IBC assists the institution to ensure that all research activities involving biosecurity-regulated materials (including SSBAs and imported materials), biologically-hazardous materials, GMOs and dual-use research of concern, and facility licensing and approvals, are in accordance with all relevant legislation, standards (including the ANZ Standard), codes of practice and licensing requirements.
- Approval from the Office of the Gene Technology (OGTR).
- Approval from the Animal Ethics Committee (AEC).
- Approval from the Human Research Ethics Committee (HREC).
- Conduct of the research in a facility with the physical containment level required for the nature of the research and as certified by the IBC and/or the OGTR. In most cases, the work was conducted in either PC3 or PC4 facilities.[i] In some cases, PC2 facilities were adequate containment for the type of research involved.
- Monitoring of the research by relevant institutional committees (AEC, HREC, IBC) and the OGTR. No unresolved issues were reported following monitoring by institutional committees.

The OGTR also independently confirmed that appropriate licences were in place for each project, where such licences were required, and relevant facilities were appropriately certified. The OGTR was also satisfied that there were no significant or unresolved issues as the result of monitoring or re-certification inspections.

Administering institutions and the OGTR also advised that appropriate monitoring and reporting took place throughout each of these projects. No incidents involving infectious agents or GMOs were reported during the conduct of the projects. For one project, an adverse event was reported to the AEC following a surgical procedure performed with mice. This issue was quickly resolved to the satisfaction of the AEC. For another project, an administrative error resulted in the incorrect facility being nominated in an application for a licence issued by the OGTR. The facility that was being used was certified by the OGTR, was appropriate for the activities and was added to the OGTR licence following identification of the error.

Significantly, the review established that all controls required under Australia's regulatory framework were in place during the conduct of all the projects identified. The effectiveness of these controls appears to be supported by the absence of significant or unresolved issues following monitoring by institutional committees and the OGTR, and the absence of reported incidents involving infectious agents or genetically modified organisms during the conduct of the projects.

i PC: Physical Containment

PART 4: International comparisons

Part 4 compares Australia's framework for the regulation and oversight of research, as outlined earlier in Part 2, with the frameworks in other relevant countries (**Section 6: International regulatory frameworks**).

An overview of international reviews and analyses about biosafety and biosecurity is also provided (**Section 7: International reviews and analyses**).

The information presented in this part of the report is based on information sourced from Australian Government agencies that are responsible for the regulation and oversight of biological research, as well as from international reports and academic literature.

Key points

International regulatory frameworks

- Australia's framework for the regulation and oversight of research involving relevant research (such as research involving infectious agents or GMOs) is both comprehensive and generally comparable to frameworks in other relevant countries. The framework is informed by international standards, guidelines and treaties.
- In some areas, including research involving animals or using human biospecimens (tissues and cells), Australia has no national legislation (unlike many comparable countries) but Australia does have national guidelines that are comparable to other countries.
- Australia's framework, like comparable countries, incorporates internationally accepted principles and practices for the ethical and humane use of animals for research.
- In Australia and comparable countries, oversight of research using human biospecimens is by research ethics review committees and/or institutional governance processes with reference to broad standards governing the conduct of human research.
- Australia's export control framework is harmonised with like-minded countries and multilateral export control regimes and operates to ensure that exports do not contribute to the development of chemical and biological weapons. Australia's control list includes human pathogens, GMOs, biological agents and other relevant goods and technologies.
- Australia's SSBA Regulatory Scheme, which provides a framework for the containment of dangerous pathogens and toxins, is internationally recognised and has been used as a model in similar countries.
- Australia regulates both commercial and research use of GMOs, while Canada and the USA only regulate a GMO once it is considered for commercial release. Australia has specific legislation for laboratory-based research with GMOs and the Gene Technology Regulator certifies facilities undertaking such research.

International reviews and analyses

- In the 2021 Global Health Security (GHS) Index, out of 195 countries, Australia ranked 2nd overall and 7th in the category of the prevention of the emergence or release of pathogens, which includes indicators such as biosecurity, biosafety, dual-use research and the culture of scientific research. While the GHS Index does not predict the performance of different countries during a crisis such as the COVID-19 pandemic, it is nonetheless an independent assessment on an international scale that measures the tools and resources countries have to prevent, detect and prepare for biosecurity and biosafety risks.
- When last assessed by the World Health Organization (WHO) in 2017, Australia's approach to implementing the *International Health Regulations (2005)* was described as a benchmark for other countries in the management of biorisks, both of natural and intentional causes.
- The risk assessment and management practices for biosafety and biosecurity in Australia and comparable countries were described in 2020 as 'embedded in a vast and robust framework of international, regional and national regulations' dealing with the safe handling of organisms under contained use, including GMOs.[89]
- The ANZ Standard *Safety in laboratories*, including requirements for working with pathogens requiring physical containment levels 3 and 4 (or biosafety levels 3 and 4), is comparable to national biosafety requirements in other countries. Some countries – including Australia – provide additional useful guidance on the roles, responsibilities and qualifications required by principal investigators and biosafety professionals, which is a useful pillar in building an organisational culture of safety.

6. International regulatory frameworks

This section summarises the frameworks for the regulation and oversight of research internationally and compares the frameworks for the regulation and oversight of research in Australia with those in other relevant countries. Relevant countries included in this comparison are: Canada, Denmark, European Union (EU), Japan, India, New Zealand, Singapore, United Kingdom (UK) and the United States of America (USA). These countries were selected for comparison as they are routinely used as benchmarks for the following areas of research:

- Use of animals (**Section 6.1.1**)
- Use of human tissues or cells (**Section 6.1.2**)
- Controlled goods and technology, including dual-use items (**Section 6.1.3**)
- Security sensitive biological agents (**Section 6.1.4**)
- Biological Weapons Convention (**Section 6.1.5**)
- Use of genetically modified organisms (**Section 6.1.6**).

The existence or otherwise of key elements in each area of the framework is appraised and compared with the regulatory framework in Australia. Information in this section includes reference to relevant international standards, guidelines and treaties.

6.1 International frameworks governing specific aspects of life sciences

6.1.1 Use of animals

Most countries, including Australia, have incorporated internationally accepted principles and practices for the ethical and humane use of animals for research. These principles are outlined in the *International Guiding Principles for Biomedical Research Involving Animals*, developed by the International Council for Laboratory Animal Science (ICLAS) and the Council for International Organizations of Medical Sciences (CIOMS).[90] They include the need for justification for animal use, the application of the 3Rs (Replacement, Reduction and Refinement of animal use) and the necessity for prior approval from an animal ethics committee. Most countries have also incorporated internationally accepted standards for animal care and welfare and are working towards global harmonisation – for example, those promoted through the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International) voluntary assessment and accreditation programs.[91,92]

A summary comparison of the frameworks in Australia with those in other relevant countries is provided in **Table 10**.

Table 10. Use of animals

Element	Australia	New Zealand	USA	Canada	EU	UK
Legislation	✓ State and territory legislation; no national legislation	✓ National legislation	✓ National legislation	x Policies and guidance only. Canadian Council on Animal Care (CCAC) plays central role in self-governance and oversight	✓ European Directive, with national legislation in each member state	✓ National
Animal species covered:	✓	✓	✓	✓	✓	✓
• live non-human vertebrates	Exception: Fish (SA and WA)		Exceptions: Fish, birds, rats, mice			
• cephalopods	✓	✓	x	✓	✓	✓

Element	Australia	New Zealand	USA	Canada	EU	UK
• other	✓ Decapods (Vic), Malacostraca (Qld)	✓ Crab, lobster, crayfish	X	X	X	X
Licensing[j] of institutions	✓	✓	✓	✓	✓	✓
Licensing[j] of animal facilities and/or animal care programs	✓	✓	✓	✓	✓	✓
Authorisation[j] of researchers	✓	X	✓	✓	✓	✓
Review and approval of care and use of animals by AEC or equivalent body	✓	✓	✓	✓	✓	✓
Inspections and monitoring of approved projects by AEC or equivalent body	✓	✓	✓	✓	✓	X May choose to conduct inspections
Inspections by regulatory authority	✓	✓	✓	X Inspections by CCAC	✓	✓
Mandatory training and competence of personnel	✓	✓	✓	✓	✓	✓
National training programs	✓ Institutional based; no national framework (except for animal technicians)	✓ Institutional based; no national framework	✓ Institutional based	✓	✓ EU Directive. Education and training framework	✓
Penalties for non-compliance	✓	✓	✓	X Not specific.	✓ Legislation in member countries	✓

j Terms used to describe this concept include licensing, accreditation, authorisation and certification.

6.1.2 Use of human tissues or cells

Internationally, human research is governed by laws, rules, guidelines and/or policy. This applies to the use of human biospecimens, such as tissues or cells. In Australia and other countries listed in Table 11, oversight of research using human biospecimens is predominantly by research ethics review committees and/or institutional governance processes with reference to broad standards governing the conduct of human research. The exception to this is national oversight of research involving embryos, gametes and stem cell lines. In the countries listed in Table 11, these areas of research are governed by both legislation and guidelines. However, the applicability of the legislation depends on the following factors, with countries placing differing emphasis on each of these factors:

- the source of the biospecimens (embryo or other)
- if the biospecimen is an embryo, the origin/proposed use of the embryo (for example, excess to reproductive purposes or created specifically for research purposes)
- the character of the stem cell lines (pluripotent or not).

A summary comparison of the frameworks in Australia with those in other relevant countries is provided in **Table 11**.

Table 11. Human research

The information in this table includes laboratory biospecimen/cell-based research. It excludes: (a) clinical trials or other health research with human participants, (b) 'data-only' biomedical research or (c) non-biomedical research. Further information on regulation of clinical trials or other health research with human participants, especially with reference to research involving biologicals, is available from the TGA.[93,94]

Element	Australia	New Zealand	USA	Canada	EU	UK
Type of research covered						
tissue, cell line or cellular (does not include micro-organisms)	✓ National guidelines; state and territory legislation (Human Tissue Acts) and policy	✓ National guidelines	✓ National legislation and guidelines	✓ National guidelines	✓ Legislation and/ or guidelines vary from member to member	✓ National guidelines; regulation by Human Tissue Authority (HTA)
somatic stem cell / induced pluripotent stem cell (iPSC)	✓ National guidelines (not specific to somatic/iPSC)	✓ National guidelines (not specific to somatic/iPSC)	✓ National legislation and guidelines (not specific to somatic/ iPSC)	✓ National guidelines (not specific to somatic/iPSC)	✓ Legislation and/ or guidelines vary from member to member	✓ National guidelines (not specific to somatic/iPSC)

Element	Australia	New Zealand	USA	Canada	EU	UK
embryonic stem cell /embryo / gametes	✓ National legislation (human embryos, human cloning); national guidelines (assisted reproductive technology)	✓ National legislation and guidelines	✓ Legislation varies from state to state; non-government (e.g. peak body) guidelines	✓ National legislation and guidelines	✓ Legislation varies from member to member	✓ National legislation and guidelines
Type of oversight						
Authorisation or scrutiny by regulatory authority	✓(embryos only) Research involving embryos is regulated by NHMRC's Embryo Research Licensing Committee (ERLC)	X	No evidence available	No evidence available	✓ Possible, but nature and extent not clear and would vary from member to member	✓ Probably oversight by HTA, but nature and extent not clear
Ethics approval and institutional authorisation of research	✓	✓	No evidence available	No evidence available	No evidence available	✓
Post-approval monitoring	✓ Institution and Human Research Ethics Committee (HREC) share responsibility, generally via review of amendments and annual reporting ERLC monitors embryo research licences	No evidence available	No evidence available	No evidence available	No evidence available	✓ Research Ethics Committee monitoring. Embryo research monitored by Human Fertilisation and Embryology Authority (HFEA)

6.1.3 Controlled goods and technology including dual-use items

Australia is a Participating State in a number of multilateral export control regimes. These regimes are committed to establishing best practice and consistency in the export control frameworks of participating states. Australia participates in four major multilateral export control regimes: the Australia Group (AG), Missile Technology Control Regime, Nuclear Suppliers Group and the Wassenaar Arrangement on Export Controls for Conventional Arms and Dual-Use Goods and Technologies.[95] The majority of the controls that relate to gain-of-function research are derived from the AG lists. The AG is an informal forum of countries that, through the harmonisation of export controls, seeks to ensure that exports do not contribute to the development of chemical or biological weapons. It is important to note that, while countries seek to harmonise approaches to export controls, the application of the control lists at the domestic level can vary subject to national interpretation/legislation. Australia, as the AG permanent Chair, regularly communicates with AG participants and, in particular, like-minded countries (for example, UK, USA and Canada) to work towards the consistent application of control lists.

A summary comparison of the frameworks in Australia with those in other relevant countries is provided in **Table 12**.

Table 12. Export Controls

Element	Australia	USA	UK	Canada	New Zealand
Legislation	✓ National legislation	✓ National legislation	✓ National legislation	✓ National legislation	✓ National legislation
Australia Group membership	✓ (and member of all four export regimes)[k]	✓ (and member of all four export regimes)	✓ (and member of all four export regimes)	✓ (and member of all four export regimes)	✓ (and member of all four export regimes)
DSGL 1C351: Human pathogens, zoonoses and toxins	✓	✓			
DSGL 1C352: Animal pathogens	✓	✓			
DSGL 1C353: Genetically-modified organism (based on listed pathogens)	✓	✓			
DSGL 1C354: Plant Pathogens	✓	✓			
DSGL 1E001: Technology related to 1C	✓	✓			
ML7: Biological agents	✓	✓			

k The four export regimes are: Australia Group, Missile Technology Control Regime, Nuclear Suppliers Group and the Wassenaar Arrangement on Export Controls for Conventional Arms and Dual-Use Goods and Technologies.

Element	Australia	USA	UK	Canada	New Zealand
ML22: Technology related to ML22	✓	✓			
Intangible Transfer of Technology is controlled	✓	✓[l]			
Publishing of basic scientific research and information in the public domain is uncontrolled	✓	✓			
Penalties for non-compliance (tangible and intangible)	✓ Custodial and/or financial[m]				

6.1.4 Security Sensitive Biological Agents (SSBAs)

Australia's SSBA Regulatory Scheme is frequently recognised as a good example of the development and implementation of a framework for the containment of dangerous pathogens and toxins.[96,97] This Scheme has been used as a model for regulatory frameworks for SSBAs developed in similar countries (for example, Canada). Such programs have been established in response to an increased global awareness of and requirement for pathogen security (rather than just safety) following terrorist and bioterrorist events.[98]

The national legislative frameworks underpinning the schemes/programs of comparable countries have similar goals in preventing the deliberate release of harmful biological agents and toxins, while maintaining appropriately regulated access where there is a legitimate need (for example, preparedness, diagnostics). While comparable countries listed in Table 13 regulate defined lists of agents, no list is identical and agents of high security concern appear in all. The USA Federal Select Agent Program, jointly administered by the Centers for Disease Control and Prevention (CDC) and the Animal and Plant Health Inspection Service, regulates a tiered list of 60 agents, while Australia regulates 20 under the SSBA Scheme. Tier 1 agents in the USA and Australia are almost the same. An exception is SARS-CoV (the virus that caused the 2002–2003 SARS outbreak), which is included as a Tier 1 agent in Australia but not in the USA. Each country uses different definitions for the regulation of influenza strains of security concern.

In Australia, a facility must declare the purpose for handling each SSBA upon registration, and the Department of Health determines whether the purpose is legitimate and consistent with the national legislation. If the purpose of handling is described as 'research', a description of the nature of this research is reviewed by the Australian Intelligence Community before the handling of the SSBA is approved. The USA has a similar and thorough process with additional requirements when research is declared as the purpose for handling, referred to as 'restricted experiments'. Requirements in Canada are outlined in the *Scientific Research Policy for Human Pathogens and Toxins*.[99]

l The USA makes no distinction between intangible and tangible technology (US Department of State. Controls Tangible/Intangible. Available at: https://2009-2017.state.gov/strategictrade/practices/c43180.htm)

m Defence Export Controls takes a graduated approach to compliance and will refer matters to relevant agencies for enforcement action where there are potentially serious or wilful breaches of legislation. Compliance monitoring could include requests for records relating to exports, on-site visits, and compliance reporting against permits issued.

There is some variation in the administering agencies of Schemes, personnel security requirements, and the frequency of inspections for ongoing monitoring and compliance.

A summary comparison of the frameworks in Australia with those in other relevant countries is provided in **Table 13**.

Table 13. Security Sensitive Biological Agents

Element	Australia	USA	Canada	UK	Singapore	Denmark
Legislative framework	✓	✓	✓	✓	✓	✓
Defined list of agents	✓	✓	✓	✓	✓	✓
Purpose for handling each agent must be reported to the Scheme	✓	✓	✓	✓	✓	✓
If purpose for handling is 'research' – research rationale is reviewed and approved by the Scheme	✓	✓	✓	✓	✓	✓
Individuals handling or using agents must first undergo national security check	✓	✓	✓	✓	✓	✓
Facility licensing/registration/ certification process	✓	✓	✓	✓	✓	✓
Inspection program for monitoring and compliance	✓	✓	✓	✓	✓	✓
Mandatory training and competence of personnel	✓	✓	✓	✓	✓	✓
Penalties for non-compliance (administrative, civil and criminal)	✓	✓	✓	✓	✓	✓

6.1.5 Biological Weapons Convention

The Biological Weapons Convention (BWC) effectively prohibits the development, production, acquisition, transfer, stockpiling and use of biological and toxin weapons. The BWC is a key element in the international community's efforts to address WMD proliferation and it has established a strong norm against biological weapons. The BWC has reached almost universal membership with 183 States Parties and four Signatory States. States Parties, including Australia, to the BWC undertake '*never in any circumstances to develop, produce, stockpile or otherwise acquire or retain:*

- *microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes*
- *weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict.'*

The system of Confidence-Building Measures (CBMs) under the BWC was introduced in 1987. The objective of CBMs is to prevent or reduce the occurrence of ambiguities, doubts and suspicions and to improve international cooperation in the field of peaceful biological activities.

A summary comparison of the BWC CBMs for Australia compared to the CBMs for other relevant countries is provided in **Table 14**.

Table 14. Biological Weapons Convention (BWC): Confidence Building Measures (CBMs)

Element	Australia	USA	UK	Canada	Japan	India
State Party to BWC	✓	✓	✓	✓	✓	✓
National legislation	✓	✓	✓	✓	✓	x Not declared
Other measures	✓ Australia Group Secretariat. Security Sensitive Biological Agent Standards.	✓ Export/import of micro-organisms and toxins; Biosafety and Biosecurity including: FBI Security Risk Assessments; FBI Biosecurity Outreach; USDA Biorisk Management Policy; CDC/NIH Biosafety in Microbiological and Biomedical Laboratories (BMBL); Interim Laboratory Biosafety Guidance relevant to SARS-CoV-2.	✓ Export control guidance. The Academic Technology Approval Scheme. The Specified Animal Pathogens Order 2008. Guidance for licence holders on the containment and control of specified animal pathogens.	✓ Canadian Biosafety Standard. Member of the Australia Group export control regime. Under regulations, licence holders must have a Biosecurity Plan, based on a threat and risk assessment specific for the facility.	x Not declared	x Not declared
Declare offensive or defensive R&D programs	✓	✓	✓	✓	✓	x Not declared
Declare vaccine production facilities	✓	✓	✓	✓	✓	x Not declared
Exchange of information on outbreaks of infectious diseases	✓	✓	✓	✓	x Not declared	x Not declared

6.1.6 Genetically modified organisms

Internationally, regulation of genetically modified organisms (GMOs) varies quite considerably. Some countries, including Australia, regulate both commercial and research stages, including laboratory activities, while others, such as Canada and the USA, only regulate a GMO once it is considered for commercial release. The countries examined vary in how they take risk into consideration when regulating laboratory research with GMOs. In some countries, risk is addressed through legislation specific for research with GMOs in containment, whereas in others, risk from contained GMO research is addressed through frameworks for health and safety considerations for the personnel involved in all research (GM and non-GM) and for the environment.

A summary comparison of the frameworks in Australia with those in other relevant countries is provided in **Table 15**.

Table 15. Genetically modified organisms

Element	Australia	New Zealand	USA	Canada	UK	EU
Regulation of commercial activities with GMOs	✓	✓	✓	✓	✓	✓ European Directive[n]
Specific legislation for laboratory-based research with GMOs	✓	✓	X	X	✓	✓ European Directive
Institutional oversight activities	✓	✓	N/A[o]	N/A	✓	✓
Risk tiering of authorisations	✓	✓	N/A	N/A	✓	✓
Certification of facilities	✓	✓	N/A	N/A	X Notification only	X Notification with consideration of the facility in which the GMO will be contained[p]

n The EU publishes a range of directives setting out objectives to be achieved by individual countries as they see fit.

o All references to N/A in this table reflect the absence of specific legislation for regulation of laboratory-based research with GMOs. Other frameworks for health and safety considerations for the personnel involved, and for the environment, would apply.

p Any person, before undertaking for the first time the contained use of a GMO in a particular installation, should forward a notification to the competent authority (in the individual EU member state) so that the authority may satisfy itself that the proposed installation is appropriate for the purposes of carrying out the activity in a manner that does not present a hazard to human health and the environment.

Element	Australia	New Zealand	USA	Canada	UK	EU
Accreditation of organisations	✓	✓ Facility 'Operator'[q] must be approved	N/A	N/A	X	X
Public records	✓[r]	X	N/A	N/A	✓	X
Compliance enforcement	✓	✓	N/A	N/A	✓	✓ Undertaken by Member States

q The Operator of a facility is a person, normally an individual (e.g. business owner, director or manager), but may be the Crown, a corporation sole, or a body of persons (whether incorporated or unincorporated).

r Except exempt dealings under Schedule 2 of the Gene Technology Regulations 2001.

7. International reviews and analyses

This section provides an overview of relatively recent international reviews and analyses about biosafety and biosecurity.

7.1 Global Health Security Index

The 2021 Global Health Security (GHS) Index is an independent assessment and benchmarking of health security and related capabilities across the 195 States Parties to the *International Health Regulations (2005)*.[100] The 171 GHS Index questions are organised across six categories and 37 indicators, which are used to assess a country's capability to prevent and mitigate epidemics and pandemics. The category that is most relevant to this report is Category 1: *Prevention of the emergence or release of pathogens*. Several indicators in this category are a measure of biosecurity and biosafety related to the use of dangerous microorganisms for research purposes, including dual-use research of concern, and facilities where they are stored and used, as well as national planning, surveillance and reporting for diseases that are naturally transmitted from animals to humans (zoonotic diseases).

Overall, Australia ranked 2nd amongst all 195 countries. In Category 1 (with indicators relevant to this report), Australia ranked 7th amongst all 195 countries.

While the GHS Index is an independent assessment of each countries' health security capabilities, it relies entirely on open-source information: data that a country has published on its own or has reported to or been reported by an international entity. The data were captured between August 2020 and June 2021 during a period when countries wrestled with the COVID-19 pandemic. Compared to the 2019 GHS Index[101], a revised framework and updated data collection were used to obtain information about pandemic preparedness while assessing and benchmarking health security capacities across the 195 countries. The 2021 GHS Index highlights factors that may explain why countries that received some of the top marks in the 2019 GHS Index responded poorly during the COVID-19 pandemic. The results highlight that although the GHS Index can identify preparedness resources and capacities available in a country, it cannot predict whether or how well a country will use them in a crisis. The GHS Index cannot anticipate, for example, how a country's political leaders will respond to recommendations from science and health experts or whether they will make good use of available tools or effectively coordinate within their government. The GHS Index does, however, provide evidence of the tools that countries have and the risks they need to address to protect their communities.[100]

These observations suggest that, while the overall country rankings are not predictive of performance in health crises, individual category rankings may still be broadly appropriate and reflective of areas of relative country strength.

7.2 WHO Monitoring and Evaluation Framework

The World Health Organization (WHO) has established a Monitoring and Evaluation Framework to assess country compliance with the *International Health Regulations (2005)* (IHR). One pillar of the framework is the Joint External Evaluation (JEE). Australia's JEE of IHR compliance took place during 2017. The WHO report highlighted that Australia has developed a comprehensive system of capabilities and functions to prepare, detect and respond to health security threats and has fully implemented the necessary legislation to implement the IHR. One of the most significant examples of Australia's capacity was biorisk management where Australia has been, and still is, a benchmark for other countries in the management of biorisks, both of natural and intentional causes.[102]

7.3 Regulatory overview of biosafety and biosecurity

A review of biosafety and biosecurity in containment, published in 2020, provided a regulatory overview for Australia, Brazil, Canada, EU, Singapore and USA.[89] This review concluded that the risk assessment and management practices for biosafety and biosecurity are embedded in a vast and robust framework of international, regional and national regulations and guidance dealing with handling, storage, containment measures, waste management, transport, packaging, and labelling of biological organisms under contained use, including GMOs, thereby ensuring the protection of human, animal and plant health, as well as the environment. Local (national and, regional) legislation may be influenced by policy priorities, leading to significant differences in the administrative aspects of how biosafety is regulated. However, the main principles and practices are shared worldwide. In addition, when new developments in biotechnology, microbiology and synthetic biology emerge, the existing frameworks and practices can be applied and tailored when needed.

7.4 Analysis of biosafety guidelines

A 2016 analysis provided a comparison of the biosafety guidelines published by organisations with a well-established history of biosafety policy making and practice:[103]

- Australian/New Zealand Standard *Safety in laboratories. Part 3: Microbiological safety and containment* (AS/NZS 2243.3:2010)
- Canadian Biosafety Standard, Second Edition
- European Union Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work
- Singapore Ministry of Health, Laboratory Certification Checklist and Biological Agents and Toxins Act
- United Kingdom Health and Safety Executive. The management, design and operation of microbiological containment laboratories
- United States of America. Biosafety in Microbiological and Biomedical Laboratories
- World Health Organization, Laboratory Biosafety Manual, Third Edition.

While this analysis was conducted in 2016, there have been few international comparisons of this type since that time and the results provide a useful indication of how the ANZ Standard compared with biosafety guidelines in other countries at the time of publication.

This analysis demonstrated that there are many similarities among these documents and that often differences are more due to the fact that granularity (for example, specific location of a hand washing sink) is not found in some country-specific directives, ordinances and acts. A similarity among guidance documents was that they clearly identify lines of authority for ensuring national biosafety requirements or recommendations are implemented when working with biosafety level 3 pathogens. Some countries – including Australia – provided additional useful guidance by describing roles, responsibilities and qualifications required by principal investigators and biosafety professionals, which is a useful pillar in building an organisational culture of safety.[103] Detailed comparison tables are provided in **Appendix F**.

PART 5: Conclusion

Part 5 outlines the main conclusions from the review (**Section 8: Conclusion**).

8. Conclusion

The review report notes the many uses of gain-of-function research that have resulted in significant medical innovations and benefits to human health, and outlines the strong regulatory controls in Australia that ensure research is conducted safely, ethically and responsibly.

The Australian Government has funded and/or conducted a large volume of research on infectious agents that could cause disease in humans (including potential zoonotic animal diseases) over the last decade, contributing to Australia's considerable strengths in this field.

The review found that the Government has funded through NHMRC, or conducted at CSIRO, gain-of-function research that could be categorised as 'of concern' because it involved modifying a virus or bacterium in a way that may make it more dangerous to humans. This research aimed to increase understanding and improve the detection, prevention and treatment of a range of viral and bacterial infections.

Gain-of-function research in Australia is subject to best-practice biosafety and biosecurity controls that protect both the scientists undertaking the research and the Australian community. For example, Australia has a strong regulatory framework for the use of GMOs, which includes specific national legislation for laboratory-based research with GMOs and certification of facilities undertaking such research by the Gene Technology Regulator. Australia also has world-class physical containment facilities, including CSIRO's Australian Centre for Disease Preparedness (ACDP), which is a physical containment level 4 facility designed to allow scientific research on the most dangerous infectious agents. Australia's depth of expertise in infectious disease research and the availability of high-quality biosafety containment facilities enable the safe conduct of important research to prevent, detect and protect the Australian community from the threat of infectious diseases.

PART 6: Appendices and references

9. Appendices

A. Terms of reference
B. Consultations
C. Frameworks in Australia for the regulation and oversight of research: Details
D. Methodology for the identification of relevant research
E. Categorisation of research projects by Expert Panel
F. Comparison of international biosafety guidelines

Appendix A — Terms of reference

Gain-of-function Research Review
Terms of reference

Background

'Gain of function' is a term used to describe a change to any organism through any process that causes it to acquire a new function. Certain gain-of-function experiments have raised concerns because of their potential to increase the danger posed to humans by an infectious agent, such as a virus. These concerns have been heightened by uncertainty about the origin of the SARS-CoV-2 virus responsible for the COVID-19 pandemic and suggestions that the SARS-CoV-2 virus may have been created in a laboratory as the product of gain-of-function research.

The Minister for Health and Aged Care, the Hon Greg Hunt MP, has asked the National Health and Medical Research Council (NHMRC) to undertake a review of gain-of-function research in Australia.

Purpose

The purpose of the review is to report to the Minister on:

- the definition of gain-of-function research, with particular reference to research of this nature that could pose a threat to human health
- any gain-of-function research that could increase the harmfulness of an infectious agent to humans that has been funded or conducted by the Australian Government or its agencies over the last 10 years
- the regulatory framework that controls such research in Australia, and how it compares with frameworks in other relevant countries.

Timeframe

The review will report to the Minister in December 2021.

Appendix B — Consultations

Information about Australian Government agencies consulted during the conduct of the review is provided in **Table 16**.

Table 16. Consultations

Portfolio[s]	Agency	Summary of activities
Agriculture, Water and the Environment	Department of Agriculture, Water and the Environment (DAWE)	DAWE's purpose is to enhance Australia's agriculture, environment, heritage and water resources through regulation and partnership. DAWE provide grants and invests in new initiatives to help boost productivity and exports, protect our environment and heritage and promote climate action. Relevant regulatory responsibilities include pest and disease risks of goods, people and vessels arriving in Australia, agricultural goods exported from Australia, and import and export of wildlife.[104] Relevant regulatory responsibilities include *Biosecurity Act 2015, Biological Control Act 1984*.[105]
Defence	Department of Defence	The Department of Defence deals with defence, including international defence relations and defence co-operation, defence scientific research and development, defence procurement and purchasing, and defence industry development and co-operation. Research areas include: • Air, land and sea vehicles • Autonomous systems • Chemical, biological, radiological & nuclear • Cyber • Electronic warfare • Human science • Information and communications • Operations analysis • Propulsion and energy • Surveillance and space • Weapons systems.[106] Relevant regulatory responsibilities include *Customs Act 1901, Defence Trade Controls Act 2012* and *Weapons of Mass Destruction (Prevention of Proliferation) Act 1995*.[105]
Education, Skills and Employment	Department of Education, Skills and Employment (DESE)	DESE leads implementation on national policy and programs including supporting the early childhood education and care and schooling systems and enabling students to access the higher education and skills they need to maximise employment opportunities. Current research programs and initiatives include: • Research Support program to ease the immediate financial pressures on universities caused by COVID-19 • Strategic University Reform Fund • Research Infrastructure Investment Plan • University Research Commercialisation Scheme • Centre for Augmented Reasoning.[107]

s Australian Government Department of Finance. Flipchart and list of Commonwealth entities and companies. Retrieved 12 November 2021 from: https://www.finance.gov.au/government/managing-commonwealth-resources/structure-australian-government-public-sector/pgpa-act-flipchart-and-list

Portfolio[s]	Agency	Summary of activities
Education, Skills and Employment	Australian Research Council (ARC)	The ARC advises the Australian Government on research matters, administers the National Competitive Grants Program, a significant component of Australia's investment in research and development, and has responsibility for Excellence in Research for Australia. The ARC supports research and research training through national competition in all fields of science, social sciences and the humanities, and brokers partnerships between researchers and industry, government, community organisations and the international community.[108]
Foreign Affairs and Trade	Department of Foreign Affairs and Trade (DFAT)	DFAT promotes and protects Australia's international interests to support our security and prosperity. DFAT works with international partners and other countries to tackle global challenges, increase trade and investment opportunities, protect international rules, keep our region stable and help Australians overseas.[109]
Foreign Affairs and Trade	Australian Centre for International Agricultural Research (ACIAR)	ACIAR supports research projects in four regions—eastern and southern Africa, East Asia, South and West Asia and the Pacific. ACIAR's research projects focus on agribusiness, climate change, crops, fisheries, forestry, horticulture, livestock systems, social systems, soil and land management and water.[110]
Health	Department of Health	The Department of Health works to deliver an affordable, quality health and aged care system and better health, ageing and sport outcomes for all Australians. The Department funds research to inform the development of policy for health, aged care and sport, and to assist with monitoring and evaluation of the Department's initiatives and programs. Research funded by the Department includes: • trends and risk factors of different diseases • how different treatments affect patient outcomes • new technologies • health care costs • the health status of different groups of people.[111] Relevant regulatory responsibilities include *Biosecurity Act 2015, Gene Technology Act 2000, National Health Security Act 2007* and *Therapeutic Goods Act 1989*.[105]
Health	National Health and Medical Research Council (NHMRC)	NHMRC's legislated functions are to fund health and medical research and training, and to issue guidelines and advise on improving health outcomes, through prevention, diagnosis and treatment of disease and the provision of health care. NHMRC also has a role in promoting the highest standards of ethics and integrity in health and medical research.[112]
Health	Office of the Gene Technology Regulator (OGTR)	The OGTR supports the Gene Technology (GT) Regulator, who is an independent statutory office holder responsible for administering the *Gene Technology Act 2000* and corresponding state and territory laws. The GT Regulator has specific responsibility to protect the health and safety of people, and to protect the environment from any risks posed by gene technology.[113]

Portfolio[s]	Agency	Summary of activities
Industry, Science, Energy and Resources	Department of Industry, Science, Energy and Resources (DISER)	DISER supports productivity and economic growth, and job creation for all Australians by investing in science, technology and commercialisation and growing innovative and competitive businesses, industries and regions. Activities related to investing in science, technology and commercialisation (Activity 1.1) include: • Supporting and capitalising on national science expertise to drive innovation, enhance productivity and generate globally competitive solutions across the economy to improve Australia's response to COVID-19 as well as addressing national and international challenges, such as in space, cyber, health, energy, climate change, resources, agriculture, disaster management and artificial intelligence. • Promoting the growth of a highly skilled workforce through greater understanding, awareness and participation in science, technology, engineering and mathematics (STEM), particularly for women, Aboriginal and Torres Strait Islander Peoples and other underrepresented groups. • Supporting basic research, business research and development, commercialisation and translation of research, and access to early-stage finance, and encouraging collaboration between industry and the research sector, including through Australia's world-class science agencies, and infrastructure. • Enabling Australia's participation in world-leading science, supporting access to domestic and international science facilities and deepening international science engagement to drive Australia's national interests. • DISER's public research institutions include the Commonwealth Scientific and Industrial Research Organisation (CSIRO), Australian Institute of Marine Science (AIMS), Australian Nuclear Science and Technology Organisation (ANSTO), National Measurement Institute (NMI), and Geoscience Australia.[114]
Industry, Science, Energy and Resources	Commonwealth Scientific and Industrial Research Organisation (CSIRO)	CSIRO carries out scientific research for purposes including assisting Australian industry, furthering the interests of the Australian community, and contributing to the achievement of Australian national objectives or the performance of the national and international responsibilities of the Commonwealth. CSIRO also encourages or facilitates the application or utilisation of the results of such research. Its function also includes international scientific liaison, training of research workers, publication of research results, technology transfer of other research, provision of scientific services and dissemination of information about science and technology.[115] The Australian Centre for Disease Preparedness (formerly known as the Australian Animal Health Laboratory) helps protect Australia's multi-billion dollar livestock and aquaculture industries, and the general public, from emerging infectious disease threats. It is a high-containment facility designed to allow scientific research into the most dangerous infectious agents in the world.[116]

Portfolio[s]	Agency	Summary of activities
Prime Minister and Cabinet	Department of the Prime Minister and Cabinet	The Department of the Prime Minister and Cabinet (PM&C) has six purposes and supporting priorities that reflect where the Department's efforts are focused to deliver the Australian Government's priorities. • Growing our economy, incomes and creating jobs • Vibrant and resilient regions • Strengthening families and communities • Advancing Australia's international interests and enhancing national security • Governing well • Preparing well to respond to critical issues.[117]

Appendix C — Frameworks in Australia for the regulation and oversight of research: Details

This appendix provides details of the framework in Australia for the regulation and oversight of life sciences research. It is structured as follows:

- **Section C.1**: Legislation and controls that apply to life sciences research in general
- **Section C.2**: Additional legislation and controls for life sciences research involving infectious agents, including those that may harm humans
- **Section C.3**: Additional legislation and controls for life sciences research involving modification to the genome
- **Section C.4**: Laboratories and facilities – Certification and licensing.

C.1 Life sciences research: Legislation and controls

This section outlines the legislation and external controls that apply to life sciences research in general, which include research involving modification to the genome and research involving infectious agents.

C.1.1 Work health and safety

All research in Australia must comply with Commonwealth, state and territory legislation for work health and safety (WHS). Australia's WHS laws cover biological hazards – organic substances that pose a threat to the health of humans and other living organisms. Further information is provided in **Section C.2.1**.

Australia has model WHS laws, which are developed and administered by Safe Work Australia and form the basis of the WHS Acts implemented in most jurisdictions, including the Commonwealth. The Australian Government works closely with the state and territory governments through Safe Work Australia to develop and maintain the model WHS laws. These comprise the model WHS Act, model Regulations and model Codes of Practice. State and territory WHS regulators are responsible for enforcing and regulating Australia's WHS law. In the Commonwealth jurisdiction, the regulator is Comcare.[118]

C.1.2 Use of animals

State and territory legislation for the use of animals

In Australia, the care and use of animals for research is regulated under state and territory legislation. The *Australian code for the care and use of animals for scientific purposes* (the Code)[119] which is published by NHMRC, is adopted under legislation in all states and territories. The Code is endorsed by NHMRC, the Australian Research Council (ARC), Commonwealth Scientific and Industrial Research Organisation (CSIRO) and Universities Australia (UA).

The legislation applies to all activities that involve the care and use of animals for scientific purposes including the acquisition, transport, breeding, housing and husbandry of those animals. 'Scientific purposes' includes research as well as teaching, field trials, environmental studies, diagnosis, product testing and the production of biological products. Where research involves the use of animal cell lines, the legislation applies only if live animals are used as a source for the tissues or cells used to create the cell lines. The legislation applies to the use of any live non-human vertebrate and cephalopods, with minor state-based exceptions.

Key components of the legislative framework include:

- licensing or accreditation of institutions that wish to conduct animal research, and institutions or facilities that obtain, breed, supply, transport and/or house animals used for research, by state or territory regulatory authorities
- authorisation of individuals before they can conduct animal research, either by state or territory regulatory authorities or by an institutional animal ethics committee (AEC)
- institutional responsibility for ensuring that the care and use of animals for research is conducted in compliance with relevant legislation and the Code
- approval for research involving the use of animals, and for housing and care of animals held in facilities, by an institutional AEC before the research commences
- monitoring by the AEC of the care and use of animals within licensed institutions including conducting inspections of animals and facilities
- regular and adverse event reporting by researchers and animal facility managers to the AEC and institution, and annual reporting by the institution to regulatory authorities
- requirement for those who care for and/or use animals to be competent in the procedures they perform, or be under the direct supervision of a person who is competent in the procedure
- requirements governing collaborative projects conducted within Australia, and projects conducted by Australian investigators and institutions in other countries
- independent external review of institutions and animal research by licensed inspectors, regulatory authorities or independent external review panels
- strict procedures for addressing non-compliance, with custodial or financial penalties available under legislation.

AECs are responsible for approving and monitoring research within licensed institutions including conducting inspections of animals and facilities. Prior to granting approval for any research involving animals, the AEC must be satisfied that the proposed research is ethically acceptable, and must balance whether the potential effects on the wellbeing of the animals involved are justified by the potential benefits of the research. The AEC must also be satisfied that the 3Rs have been applied, that is, there is no alternative to the use of animals (Replacement), the minimum numbers of animals are used (Reduction) and any harm to the animals is avoided or minimised and animal wellbeing is supported (Refinement).

State and territory policies and guidelines for the use of animals

Each state and territory has developed policies and guidelines to assist researchers, members of AECs and the managers of institutions to understand and comply with the requirements of the legislation in the respective jurisdiction. The policies and guidelines provide advice about a broad range of topics including animal care, animal supply, formal agreements between institutions sharing AECs, the operation of AECs, supervision and monitoring by AECs and specific research procedures.

Commonwealth legislation on the use of animals

Some aspects of the use of animals for scientific purposes are regulated under Commonwealth legislation:

- *Export Control Act 1982* and *Biosecurity Act 2015*, which regulates the importation and export of animals and animal products (see **Sections C.1.4** and **C.2.2.2**)
- *Environment Protection and Biodiversity Conservation Act 1999*, which applies to international movements of endangered species under the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES), including endangered species used for research.[120]

C.1.3 Human research including use of human tissues or cells

Human research is research conducted with or about people, or their data or tissues.

The National Statement on Ethical Conduct in Human Research

All research involving humans in Australia should meet the requirements of the *National Statement on Ethical Conduct in Human Research 2007, updated 2018* (National Statement).[121]

The National Statement is the principal ethical guideline setting out the requirements for the ethical design, review and conduct of human research in Australia. It is authored by NHMRC, the ARC and UA. Any federally funded human research is expected to conform to the requirements of and undergo ethical review based on the provisions of the National Statement. Human Research Ethics Committees (HRECs) review research proposals involving human participants to ensure that they are ethically acceptable and in accordance with relevant standards and guidelines, such as the National Statement. HRECs are usually established by organisations (public, not-for-profit or private) that conduct research involving humans. Universities and hospitals are the most common of these organisations.

While the National Statement is not a legal document, there are some particular circumstances where compliance with the National Statement is required by law, including matters relating to clinical trials, embryo research and research to which the *Privacy Act 1988* and the Privacy Guidelines apply. There may also be state legislation that applies to medical research conducted in Australia.

Legislation governing human research

All research involving the use of human tissues must comply with state and territory legislation governing the use of human tissues. Research involving human embryos and gametes, including the derivation of human embryonic stem cell lines, is governed by the *Research Involving Human Embryos Act 2002* (Cth) and the *Ethical guidelines on the use of assisted reproductive technology in clinical practice and research, 2017* (ART guidelines), issued by NHMRC. Research involving the derivation of embryonic stem cell lines or other products from a human embryo must be considered by an HREC as part of a licence application to the Embryo Research Licensing Committee. The legislation and ART guidelines do not regulate the use of these products after they have been derived. Once human biospecimens have been derived from human embryos, gametes or foetuses, the requirements of the National Statement apply for any subsequent use in research.

All research involving the administration of drugs, chemical agents or vaccines to humans or devices in humans must be considered by an HREC to assess the appropriateness of their use. If such research is part of an Australian-based clinical trial, then it may need to be disclosed to or approved by the TGA, which administers the Clinical Trials Notification (CTN)/Approval (CTA) schemes. This does not apply to clinical trials in which registered or listed medicines or medical devices are used within the conditions of their marketing approval.

In the case of multi-centre human research, the relevant institutions and their HRECs may agree that the primary ethical and scientific assessment be made at one institution/organisation, with notification of the approval to the other institutions/organisations involved in the research project (National Certification Scheme of Institutional Processes Related to the Ethical Review of Multi-centre Research).

C.1.4 Controlled goods and technology including dual-use items[122,123]

Australia's system for the regulation of the export and supply of controlled goods and technologies is part of an international and national effort to stem the proliferation of conventional, chemical, biological and nuclear weapons and the systems that deliver them. It applies to the physical export, intangible (electronic) supply, publication or brokering of goods, software or technology specified in the Defence and Strategic Goods List (DSGL), which includes goods, software and technology that may be associated with life science research.

Basic scientific research and information that is already in the public domain is exempt from export controls.

Legislation governing controlled goods and technology

Controlled goods and technology are regulated under the:

- *Defence Trade Controls Act 2012*, which controls the intangible (electronic) supply, publication of technology and the brokering of goods and technology listed on the DSGL.
- *Customs Act 1901* and associated Customs (Prohibited Exports) Regulations 1958, which controls the export of tangible (physical) defence and strategic dual-use goods and technologies listed on the DSGL.
- *Weapons of Mass Destruction (Prevention of Proliferation) Act 1995*, which provides 'catch all' controls over the export of an otherwise 'uncontrolled' item or technology that may support a Weapons of Mass Destruction (WMD) program, or be used by a military in a way that is not in Australia's national interests.

Australia's export control list, the DSGL specifies the goods, software and technology that are controlled when exported, supplied, brokered or published. Australia's export control policies and procedures are reviewed regularly to reflect shifts in strategic priorities and reflect changes in the various international counter-proliferation multilateral and export control regimes of which Australia is a member, including the Australia Group (AG) and the Proliferation Security Initiative.

Defence Export Controls (DEC) within the Department of Defence is Australia's military and dual-use goods and technology export regulator. DEC's responsibilities include:

- assessing applications to export, supply, publish or broker military and dual-use goods and technology listed on the DSGL
- issuing authorisations (permits or licences) to export, supply, publish or broker military and dual-use goods and technology when they are determined as not prejudicial to Australia's defence, security or international relationships
- proactively prohibiting the export, supply or provision of goods, technologies or services that may be used in, or assist, a WMD program
- conducting compliance activities to ensure permit and licence holders comply with conditions and requirements.[124]

Australia's Defence and Strategic Goods List (DSGL)

The DSGL comprises two parts– Part 1 which lists controlled military items, and Part 2 which lists controlled dual-use items. Biological materials may be listed under Parts 1 or 2 of the DSGL.

Part 1 of the DSGL:

- Biological weapon agents, that is, biological materials that are adapted or configured to produce casualties in humans or animals, degrade equipment or damage crops or the environment.
- Software and technology for the development, production and use of listed biological weapon agents.

Part 2 of the DSGL:

- Dual-use controlled biological material (human pathogens, including viruses, bacteria, toxins and fungi; animal pathogens, including viruses and mycoplasmas; plant pathogens, including viruses, bacteria and fungi). The controls apply to natural (wild type), enhanced and modified (including genetically modified) biological materials; those made via synthetic biology; and both isolated live cultures and deliberately inoculated or contaminated living material. Written nucleic acid sequences of controlled biological materials are not controlled.
- Technology for the development and production of listed dual-use biological materials. However, there are no controls on technology that is for the use of a pathogen.
- Genetic elements and genetically modified organisms that contain nucleic acid sequences from DSGL-listed pathogens that are either associated with pathogenicity (either increasing or decreasing pathogenicity) or are responsible for the coding of DSGL-listed toxins. To future-proof for advances in emerging technologies, such as synthetic biology, controlled pathogens remain controlled even if they have been inactivated (unless it can be confirmed by the exporter that sufficient disruption has taken place that no infectious nucleic acid fragments remain).
- Vaccines are exempt from control if they are in a pharmaceutical formulation that is licensed by, or has marketing or clinical trial authorisation by, a regulatory authority.

C.1.5 Therapeutic Goods

The TGA regulates therapeutic goods for human use under the *Therapeutic Goods Act 1989* and the Therapeutic Goods Regulations 1990. The regulatory framework is based on a risk management approach designed to protect public health and safety, while avoiding any unnecessary regulatory burden. The Act covers the import, manufacture, supply and export of therapeutic goods such as herbal medicines, prescription medicines, biologicals, vaccines and medical devices to ensure their safety, quality and efficacy. Therapeutic goods include pathogenic microorganisms where these are included in vaccines for human use and which may be used in research about the vaccines.[125,126] The TGA also has a role in regulating clinical trials in Australia that involve the use of 'unapproved' therapeutic goods, to ensure the safety of participants.

C.1.6 Funding agencies

Peer review of applications for funding

Peer review provides impartial and independent expert scrutiny of proposed research and helps to maintain high standards in research. It is a system used in Australia and internationally for assessment of research proposals and grant applications. Funding agencies such as NHMRC and the ARC do not fund research unless the work is of high quality, as determined by the funding body's peer review process.[83]

Grants and contracts

Funding agencies such as NHMRC and the ARC require all research that they fund to comply with all relevant legislation (Commonwealth and state and territory) as well as appropriate ethical, legal and professional frameworks, obligations and standards. Requirements also include prior approval before work commences from institutional ethics and biosafety committees – for example, AECs, HRECs and/or Institutional Biosafety Committees. These requirements are a condition of funding and are outlined in the funding agreement, rules or contract between the funding agency and the institution or individual receiving the funds.

Policies, standards and guidelines

Funding agencies such as NHMRC and the ARC require compliance with policies, standards and guidelines. The *Australian Code for the Responsible Conduct of Research, 2018*[83] articulates the principles and responsibilities that underpin the conduct of Australian research. The Code is developed jointly by NHMRC, the ARC and UA.

Other policies, standards and guidelines include:[127,128]

- Australian code for the care and use of animals for scientific purposes, 2013 (updated 2021)
- National Statement on Ethical Conduct in Human Research, 2007 (updated 2018)
- Ethical guidelines on the use of assisted reproductive technology in clinical practice and research, 2017
- Principles and guidelines on the care and use of non-human primates for scientific purposes, 2016
- Funding agency policies for open access
- Funding agency policies for research integrity and misconduct.

C.1.7 Research conducted in another country

Research funded by the Australian Government and conducted in another country is normally required to comply with relevant Australian legislation, policies and standards as a minimum, provided that such compliance does not breach relevant local legislation. Local cultural values may also be relevant considerations.

C.1.8 Zoonotic diseases and notifiable diseases in humans

Detection and investigation of zoonotic diseases in animals

Zoonotic diseases are those that can be transmitted between animals and humans. State and territory departments of agriculture/primary industries and health and the Commonwealth (DAWE and the Department of Health) work in partnership to detect and respond to zoonotic disease outbreaks. This partnership has included assessments of animal disease risks to human health and agreement upon standard operating procedures and response guidelines to minimise the risks of, and to manage, zoonotic events.[129]

DAWE is responsible for national coordination on animal health matters. The Australian Veterinary Emergency Plan (AUSVETPLAN) contains the nationally agreed approach for the response to emergency animal disease incidents in Australia. Its development and review is managed by Animal Health Australia in partnership between the Australian Government and major national livestock industry organisations.[130]

Wildlife health and disease events in Australia are also monitored. Research and investigation of such events, which is coordinated by Wildlife Health Australia, assist in limiting the deleterious impact of wildlife diseases on areas such as human health.[131]

Detection and investigation of notifiable diseases in humans

The Commonwealth Department of Health, through the Office of Health Protection and Response, has overall responsibility for national communicable disease surveillance in humans. Under the *National Health Security Act 2007*, a disease is listed on the National Notifiable Disease List if an outbreak of the disease is considered to be a public health risk. State and territory health departments collect notifications of communicable diseases from doctors, hospitals and/or laboratories under their public health legislation.

The conduct of research into notifiable diseases in humans is subject to all relevant sections of the framework in Australia for the regulation and oversight of research.

C.1.9 Institutional governance and practices

This section outlines institutional governance and practices to ensure that institutions and their researchers can meet their legislative and compliance obligations for the conduct of research, including gain-of-function research. Some institutions may implement measures beyond regulatory requirements.

In the context of this report, the term 'institution' refers to any institution or organisation that conducts research funded by the Australian Government or its agencies, including universities, hospitals, research institutes, government departments or agencies, agricultural organisations, commercial companies and organisations involved in animal breeding and supply.

Institutional policies and guidelines

Institutions normally require research conducted by institutional employees and/or on behalf of the institution to comply with relevant institutional policies and guidelines, as well as relevant legislation and policies and guidelines of regulatory authorities.

Biosafety committees

An institutional committee is usually responsible for assisting the institution to ensure that all research activities involving biosecurity-regulated materials (including SSBAs and imported materials), biologically-hazardous materials, genetically modified organisms (GMOs) and dual-use research of concern are conducted in accordance with legislation, relevant standards (including the ANZ Standard), codes of practice and licensing requirements. Establishment of an Institutional Biosafety Committee (IBC), with specific requirements for membership, may be necessary as part of the institution's accreditation under the *Gene Technology Act 2000*. In some institutions, the IBC's role is limited to the use of GMOs, with an institutional safety committee being responsible for other safety and regulatory aspects of research activities. Other institutions may choose to expand the IBC's role to cover all safety and regulatory aspects of research activities, including the use of GMOs.

Institutions may also appoint Biosafety Advisors or Biosafety Officers to assist the institution to meet its regulatory obligations.

Animal ethics committees

Institutions involved with the care and use of animals for scientific purposes must be licensed or accredited under state and territory legislation to conduct research that involves the use of animals. Institutions are responsible for ensuring, through the operation of an animal ethics committee (AEC), that the care and use of animals for research is conducted in compliance with relevant state and territory legislation and the *Australian code for the care and use of animals for scientific purposes*.[119] The AEC must be constituted and functioning in accordance with the legislation. Institutions may use an external AEC or share an AEC with another institution. Institutional responsibilities include ensuring that guidelines for animal care and use, developed in consultation with the AEC, are implemented. Institutions are also required to report annually about the care and use of animals for scientific purposes conducted on behalf of the institution, including the activities of the AEC, to state and territory regulatory authorities.

Institutions may appoint officers (e.g. Animal Welfare Officer) to assist the institution to meet its regulatory obligations and ensure that the care and use of animals for scientific purposes proceeds in compliance with the decisions of the AEC.

Human Research Ethics Committees

Institutional Human Research Ethics Committees (HRECs) review research proposals involving human participants to ensure that they meet ethical standards and guidelines. These guidelines include the *National Statement on Ethical Conduct in Human Research*.[121] The National Statement requires many types of human research to undergo ethics review. It also sets out the requirements for an HREC's establishment, operation and membership.

There are approximately 200 HRECs in research organisations across Australia. NHMRC maintains a list of registered HRECs. Registration means that the HREC has notified NHMRC of its existence and declared that it meets the requirements of the National Statement.

Although organisations are responsible for the activities of their own HREC(s), NHMRC requires HRECs to report annually about their activities. NHMRC assesses annual reports for compliance with the requirements of the National Statement and notifies organisations and HRECs of the outcome. The summary data from HREC annual reports are also provided to the Australian Health Ethics Committee.[132]

Institutions may appoint Human Ethics Advisors to assist the institution to meet its regulatory obligations and ensure that human research proceeds in compliance with the decisions of the HREC.

Training

Institutions are responsible for training researchers in the ethical, regulatory and other requirements related to all aspects of research, including requirements for work health and safety, animal research, human research, gene technology, handling and use of microorganisms including SSBAs, controlled goods and technology, biosafety and biosecurity. For some aspects of research, training and competence are requirements under the relevant legislation (e.g. work health and safety, animal research, use of GMOs).

Training of researchers also includes training in fundamental research techniques such as those used for gain-of-function experiments, as well as the handling of GMOs, SSBAs or other high-risk pathogens or toxins and working in physical containment laboratories (for example, PC3 and PC4 laboratories). In addition, post-doctoral training and continuing professional development for researchers at other institutions within Australia and overseas are normal and long-standing practices in an increasingly diverse, mobile and global research environment. This approach accords with international practice for training and professional development of researchers.

C.2 Infectious agents: Additional legislation and controls

An infectious agent is a biological agent that causes disease or illness to its host. Most infectious agents are microorganisms (such as bacteria, viruses, fungi and protozoa), parasites and prions.[16]

This section outlines frameworks for the regulation and oversight of research involving infectious agents, in addition to those outlined elsewhere in this appendix.

C.2.1 Work health and safety (biosafety)

Legislation governing infectious agents and work health and safety

Australia's WHS laws cover biological hazards – organic substances that pose a threat to the health of humans and other living organisms (see **Section C.1.1**). Examples of biological hazards are pathogenic microorganisms, toxins (from biological sources), spores and bioactive substances.[133]

Safety standards for working with infectious agents

The Australian/New Zealand Standard *Safety in laboratories. Part 3: Microbiological safety and containment* (AS/NZS 2243.3:2010) (ANZ Standard) sets out requirements, responsibilities and general guidelines relating to safe handling and containment of microorganisms and prions in laboratories, including genetically modified microorganisms. The ANZ Standard is intended to assist employers and employees to meet their obligations under WHS legislation. The ANZ Standard is not required by law in any jurisdiction unless it has been specifically incorporated by an Act or regulation in that jurisdiction. However, the ANZ Standard is recognised in common law as defining current knowledge in microbiological safety practice.[23]

C.2.2 Biosecurity

C.2.2.1 Security Sensitive Biological Agents[123,134]

Security Sensitive Biological Agents (SSBAs) are biological agents and toxins that the Australian Government Minister for Health considers to be of security concern to Australia. They include any agents that may be used for a terrorist or criminal act and agents that could be developed, produced, stockpiled, acquired or retained in types and quantities that could allow the biological agent to be used as a weapon.

Legislation governing SSBAs

SSBAs in Australia are regulated under the:

- *National Health Security Act 2007* (NHS Act), which establishes the SSBA Regulatory Scheme under Part 3 for entities and facilities that handle suspected or known SSBAs.
- *National Health Security Regulations 2018* (NHS Regulations), which provide the operational detail of the SSBA Regulatory Scheme.

SSBA Regulatory Scheme

The aim of the SSBA Regulatory Scheme is to limit opportunities for acts of bioterrorism or biocrime to occur using harmful biological agents and to provide a legislative framework for managing the security of SSBAs.

The List of SSBAs sets out the biological agents that have been assessed as posing security concern to Australia.[135] The list is divided into two tiers — Tier 1 agents are those that pose the highest biosecurity risk and are subject to the highest level of security and reporting, while Tier 2 agents pose a high biosecurity risk and are subject to proportionately high security and reporting. The List of SSBAs also sets out the reportable quantities of toxins, including abrin, botulinum toxin and ricin.

All facilities that handle SSBAs on an ongoing basis are required to register with the Scheme. Upon registration, a facility must declare the purpose for handling each SSBA, and the Department of Health determines whether the purpose is legitimate and consistent with the NHS Act. If the purpose is described as 'research', a description of the nature of this research is provided by the department to the Australian Intelligence Community for review before the handling of the SSBA is approved. Registered facilities must also report any changes to the purpose for handling, including any research related changes.

The SSBA Regulatory Scheme is further strengthened through a background-checking scheme for persons who handle SSBAs. Background checks, known as National Heath Security Checks, consist of a national criminal history check against a list of disqualifying offences and a security assessment.

The SSBA Regulatory Scheme is supported by an inspection program to ensure compliance of facilities with the legislation and standards.

SSBA Standards

The SSBA Standards set out the minimum security requirements for entities and facilities that handle suspected or known SSBAs. The SSBA Standards are mandatory under the legislation governing SSBAs. Requirements are outlined for risk and incident management, personnel and physical security, information security, inactivation and decontamination, disposal, transport and management systems. The emphasis of the SSBA Standards is on biosecurity rather than biosafety, with the latter being addressed by complying with the WHS legislation (Commonwealth, state and territory) and the ANZ Standard.[136]

C.2.2.2 The *Biosecurity Act 2015* and associated regulations[123]

The Biosecurity Act 2015 and associated regulations are designed to manage the risks associated with the introduction, establishment and spread of pests and diseases affecting humans, plants, animals and the environment. It controls the import into Australia of all biological material, including those to be used for research purposes, and may prohibit import in some circumstances.

The Director of Biosecurity (DAWE) and the Director of Human Biosecurity (Department of Health) may jointly determine that specified classes of goods must not be brought or imported into Australian territory unless specified conditions are complied with, including human pathogenic microorganisms and toxins.

Import conditions may relate to the storage, transportation, distribution and disposal of goods, the use of the goods and the personnel authorised to handle or use the goods. Import conditions vary depending on the nature of the organisms and on the risks involved. High-risk organisms such as serious pathogens of humans, animals and plants, which might be considered as potential biosecurity risks, would only be permitted under the most stringent, high security conditions.

Approved Arrangements

Approved Arrangements are voluntary arrangements entered into with DAWE under the *Biosecurity Act 2015* that allow operators to manage biosecurity risks using their own sites, facilities, equipment and people, with compliance monitoring and auditing. The class of approved arrangements is based on the type of activities taking place in the arrangement and the associated biosecurity risks.[137]

Approved arrangements specify the standards for containment, disposal, facility construction, record keeping and behaviours to manage biosecurity risks. Goods directed to be held in an approved arrangement remain under Biosecurity control. Approved arrangements facilitate the importation of some infectious agents and microorganisms, where the biosecurity risks would not otherwise be managed in Australia.

C.2.2.3 *Crimes (Biological Weapons) Act 1976*[123]

The *Crimes (Biological Weapons) Act 1976* makes it unlawful for Australians to develop, produce, stockpile or otherwise acquire or retain microbial or other biological agents or toxins, whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes; or weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict. The Act extends to the acts of Australian citizens outside Australia.

The Crimes (Biological Weapons) Regulations 1980 specify the way in which substances acquired under the *Crimes (Biological Weapons) Act 1976* should be stored, disposed of and analysed.

C.3 Gene technology: Additional legislation and controls[138]

This section outlines the framework for the regulation and oversight of research involving gene technology, in addition to those outlined elsewhere in this appendix.

Gene technology provides ways to make changes to genes. Gene technology is a modern branch of biotechnology that allows direct modification or removal of a gene, or the transfer of a gene from one species to another. When plants, animals and other organisms are changed using gene technology they are known as genetically modified organisms (GMOs), for example, genetic modification of a microorganism to develop a vaccine. GMOs can be produced through recombinant DNA technology, gene editing and synthetic biology (see **Table 3**).

Commonwealth and state and territory governments regulate activities with GMOs through a nationally consistent Gene Technology Scheme (the GT Scheme). Established by an intergovernmental Gene Technology Agreement, and now led by the Gene Technology Ministers' Meeting (GTMM), the GT Scheme centres on the *Gene Technology Act 2000* (GT Act), Gene Technology Regulations 2001, and corresponding state and territory legislation.

The Object of the GT Act is 'to protect the health and safety of people and the environment by identifying risks posed by, or as a result of, gene technology, and by managing those risks through regulating certain dealings with genetically modified organisms'.

The legislation regulates all dealings (for example, research, manufacture, production, transport, destruction, commercial release or import) with live and viable GMOs. A 'dealing' with a GMO is defined in the GT Act and includes activities relevant to laboratory research and early product development with GMOs, through to commercialisation of a GMO.

C.3.1 Regulatory processes

Accredited organisations and Institutional Biosafety Committees

Accreditation of organisations that demonstrate they can effectively oversee work with GMOs helps manage risks from dealings with GMOs. All licensed dealings require the organisation undertaking the dealings to be accredited. Through the process of accreditation, the Gene Technology (GT) Regulator assesses if the organisation has the resources and the internal processes in place to enable it to oversee work with GMOs effectively.[139]

To become accredited an organisation must have established, or have access to, an appropriately constituted Institutional Biosafety Committee (IBC). IBCs provide on-site evaluation of low-risk contained dealings that do not require case-by-case consideration by the GT Regulator. IBCs are required to comprise suitable experts and an independent person, and they provide a quality assurance mechanism that reviews the information applicants submit to the GT Regulator.

Certified facilities

All dealings with a GMO that are not authorised for an intentional release into the environment must be carried out in a facility certified by the GT Regulator. The GT Regulator certifies physical containment (PC) facilities to ensure that appropriate standards are met for containment of GMOs and that trained and competent staff are carrying out the necessary procedures and practices. The classifications relate to the structural integrity of buildings, equipment use, and the handling practices employed by those working in the facility.[140]

PC1 facilities are used to contain organisms posing the lowest risk to human health and the environment, while PC4 facilities provide the most secure and stringent containment conditions. Further information regarding PC facilities is outlined in **Section C.4.2**.

GMO dealing authorisations

The GT Scheme regulates work with GMOs (GMO dealings) using a risk-based approach, where higher risk activities involving GMOs are subject to greater regulatory oversight than lower risk activities. Every dealing with a GMO needs to be licensed by the GT Regulator unless the dealing is an exempt dealing, a Notifiable Low Risk Dealing (NLRD), on the GMO Register, or specified in an Emergency Dealing Determination (EDD). Research with GMOs undertaken in containment facilities can be authorised as an exempt dealing, NLRD or licensed.

Dealings not involving intentional release licences

Dealings not involving intentional release are a category of licensed dealings with GMOs that are undertaken in containment facilities and do not meet the criteria for classification as exempt dealings or NLRDs. Contained GMO dealings require licensing if they involve specific risk factors, for example, genetic modifications that may increase the capacity of the

GMO to cause harm or higher risk unmodified parent organisms. Each licence application is subject to a comprehensive, science-based, case-by-case analysis, including preparation of a risk assessment and risk management plan.[141] The GT Regulator may only issue a licence if satisfied that any risks posed by the dealings proposed to be authorised by the licence are able to be managed in such a way as to protect the health and safety of people and the environment.

C.3.2 Monitoring and compliance

OGTR conducts regular inspections of approved facilities, trial sites and other licensed dealings to ensure that licence conditions are being met and that work with GMOs is being carried out in a manner that protects human health and safety and the environment. The OGTR undertakes routine, responsive, and strategic monitoring. The GT Act provides compliance powers to enable the GT Regulator to respond to identified noncompliance with licence conditions.

C.4 Laboratories and facilities – Certification and licensing

C.4.1 Animal facilities: Licensing

Licensing of facilities involved with the care and use of animals for research, including breeding, holding and supply of animals, is required under state and territory animal welfare legislation.

C.4.2 Physical containment/biosafety requirements

As outlined in **Sections C.1.9** and **C.3**, depending on the nature of the research, facilities where research is conducted must be licensed, certified or approved to ensure appropriate physical containment for the type of research being conducted. Facilities that handle GMOs, SSBAs or other high-risk pathogens or toxins, and imported biologicals used *in vivo* must follow the appropriate legislation and standards. Implementing and ensuring compliance with requirements, including access control and operational practices for the facility and training for facility/laboratory staff, is the responsibility of regulated facilities and institutions.

The Australian/New Zealand Standard *Safety in Laboratories. Part 3: Microbiological safety and containment (AS/NZS 2243.3:2010)* (ANZ Standard) sets out requirements for physical containment when working with microorganisms (biosafety).[23] The ANZ Standard is referenced under:

- the OGTR's guidelines for certification of facilities where certain work with GMOs must be undertaken[140,142]
- conditions for sites approved by DAWE under Approved Arrangements for activities including research, analysis and/or testing of imported biological material including micro-organisms, animal and human products (Class 5).[143]

A summary of the requirements for physical containment (PC) levels 1–4 is provided in **Table 17**. Internationally, PC levels can also be described as biosafety levels (BSL).

The SSBA Standards specify facility requirements for physical and information security for SSBAs (biosecurity). The requirements are risk based and differ depending on whether the organisms involved are Tier 1 or Tier 2 SSBAs.[136]

Table 17. Description of Physical Containment (PC) facility requirements[138,144]

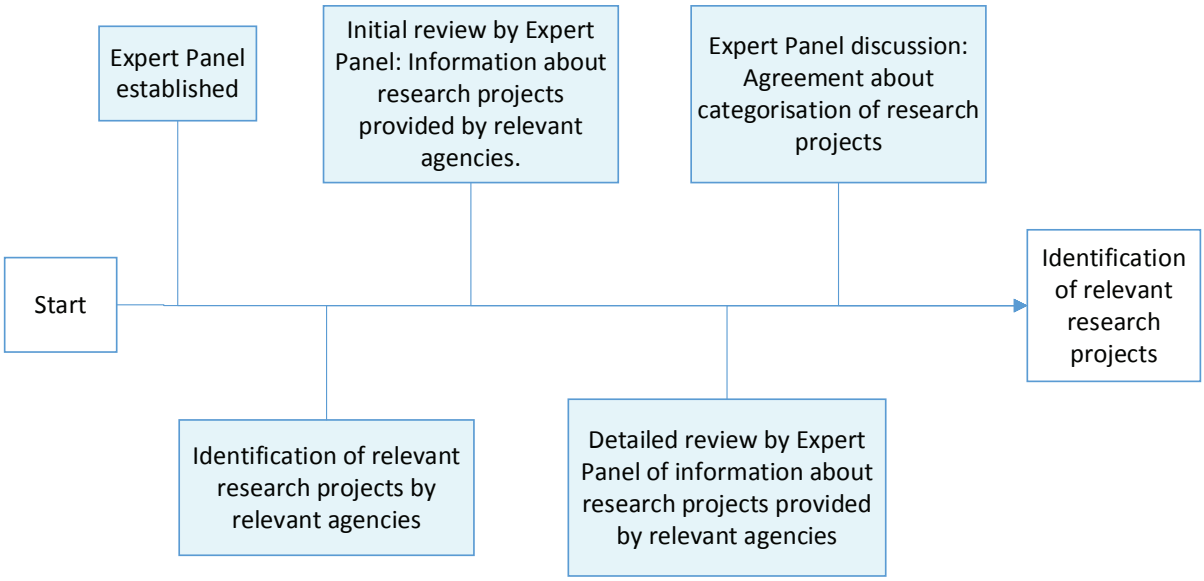
	PC1	PC2	PC3	PC4
Description	Used for work conducted on microorganisms and toxins not known to cause disease in healthy adults	Used for work conducted on microorganisms and toxins that pose a moderate risk to staff and the environment	Used for work conducted on microorganisms and toxins that can be transmitted by air and cause potentially lethal infection through respiratory transmission	Used for work conducted on microorganisms and toxins that pose a high risk of aerosol-transmitted laboratory infections with no vaccine or therapy
Laboratory practices	• Standard microbiological practices are followed • Work can be performed on an open bench or table	Access to laboratory is restricted when work is being conducted	• Laboratory access is always restricted and controlled • Laboratory access requires significant training and is carefully controlled	• Laboratory staff receive immunisations for microbes they work with (recommended) • Change clothing before entering • Shower upon exiting • Decontaminate all materials before exiting
Safety equipment	• No special equipment required • Physical Protective Equipment (PPE) (lab coats, gloves, eye protection) worn as needed	• Appropriate PPE (lab coats and gloves) must be worn • Eye protection and face shield worn as needed • Procedures that produce aerosols or splashes are performed within a Class I or Class II biological safety cabinet (BSC) (recommended) • An autoclave or alternative method is available for decontamination of laboratory waste	• Appropriate PPE (lab coats, gloves and eye protection) must be worn • Respirators worn as required • All work with biological agents must be performed in a Class I or Class II BSC	All work is performed within a Class III BSC or by wearing a full body, positive pressure, air supplied suit
Facility construction	• No special facility design required • Easily cleaned surfaces that can endure the basic chemicals used in the laboratory • A sink for handwashing must be accessible	• Hand and eye washing sink stations readily available • Lockable doors and windows	• Hands-free sink accessible near exit • Negative air pressure gradient in the facility and directional airflow into the work area. All exhaust air from the facility must be filtered. • Two sets of self-closing interlocked doors and sealed windows	Laboratory is an isolated and restricted zone Dedicated supply and exhaust air

Appendix D — Methodology for the identification of relevant research

This appendix provides further details of the methodology used to identify research that was in scope for the review (see **Section 4**) – that is, gain-of-function research that could increase the harmfulness of an infectious agent to humans and had been funded or conducted by the Australian Government or its agencies over the last 10 years. This type of research is also described in this report as 'in scope', 'relevant research' and 'gain-of-function research of concern'.

The methodology is summarised in **Figure 7** below.

Figure 7. Summary: Process for identifying research projects that were in scope for the review



D.1 Expert Panel

D.1.1 Membership

NHMRC established an Expert Panel to identify research projects that were in scope for the review. The Expert Panel comprised members with expertise relevant to infectious diseases and gain-of-function research. To ensure the independence and integrity of the process, members were nominated from across a range of government agencies (**Table 18**). NHMRC appointed one external expert scientific adviser.

Table 18. Membership of Expert Panel

Nominating Organisation	Role/Number of members[t,u]
NHMRC	Chair
Commonwealth Scientific and Industrial Research Organisation	1
Department of Agriculture, Water and the Environment	1
Department of Foreign Affairs and Trade	2
Health Portfolio	
• Health and Medical Research Office, Department of Health	4
• NHMRC (including contracted expert scientific advisor)	4
• Office of the Gene Technology Regulator	2

D.1.2 Expertise

The expertise of the Panel members included:

- antimicrobial resistance
- bacteriology
- biotechnology
- brain development
- cancer and cancer genomics
- cardiovascular disease
- gene therapy
- gene expression
- immunology
- infectious disease
- microbiology
- molecular biology
- molecular therapy
- parasitology
- proteomics
- veterinary epidemiology
- virology
- zoonotic disease.

D.1.3 Declaration of interests and management of conflicts of interest

Disclosures of interests and management of conflicts of interest for the Expert Panel were undertaken in accordance with the requirements of the *National Health and Medical Research Act (1992)* and NHMRC's *Policy on the disclosure of interest requirements for prospective and appointed NHMRC committee members*.[87] The aim of this process was to ensure that Expert Panel members, observers and other NHMRC staff (including NHMRC's CEO) were not involved in discussions or decisions about a research project with which they had any interest or involvement. As outlined in NHMRC's Policy, key elements of this process were as follows.

During allocation and review of projects

Members of the Expert Panel were required to disclose interests prior to allocation of any research projects for review. Projects were not allocated to members who had disclosed an interest in the project. Members were also required to disclose interests at any point following allocation of projects for review if they subsequently became aware of an interest relevant to a project. In this instance, the project was allocated to another Expert Panel member for review.

t The number of members varied slightly during the process depending on their other commitments.
u A representative from the Australian Research Council participated as an observer.

During meetings of the Expert Panel

Disclosures of interests and management of any conflicts of interest were a critical part of every meeting of the Expert Panel. At the beginning of every meeting, members were asked to disclose any interests relevant to the matters under discussions. In addition, members were asked to disclose interests relevant to a project before any discussion of the project commenced.

If an interest was disclosed in a matter to be discussed, the Expert Panel determined whether the member who disclosed the interest may participate in the discussion and decisions about the matter. If it was determined that the member should not participate, the member withdrew from the meeting during the discussion and decisions. As all meetings of the Expert Panel were held via videoconference, this was achieved by transferring the member to the virtual Waiting Room for the entire discussion of the matter.

These procedures were also followed for NHMRC's CEO when present as an observer to an Expert Panel meeting.

D.2 Information provided by Australian Government agencies

As outlined in **Section 4.2: Identifying relevant infectious disease research projects** and **Section 5: Results**, Australian Government agencies provided information about research projects that met the inclusion criteria, for review by the Expert Panel. Information provided to enable the Expert Panel to make a determination about research projects included:

- project title
- project synopsis
- project level data including key words and Field of Research (FoR) codes where they were available and any other relevant information or classification of research projects[145]
- additional information as required for detailed review including project plan, final report to the funding agency and/or research outputs such as publications.

D.3 Review by the Expert Panel

Information about research projects provided by relevant Australian government agencies was reviewed by the Expert Panel to identify projects that were in scope for the review. Information about the decision-making by the Expert Panel is provided in **Section 4.3**.

D.3.1 Allocation of research projects to members for review

Research projects were allocated for review by Expert Panel members, taking into account the disclosed interests and expertise of members. Expert Panel members disclosed interests prior to allocation of research projects for their review and were not allocated projects for which they had disclosed an interest. Members were also able to disclose interests at any point following allocation of projects for review if they became aware of an interest in a project once they received detailed information about that project.

Where an Expert Panel member advised that they were unable to review a project allocated to them because of an interest in the project, or because of lack of appropriate expertise in the subject matter, the project was allocated to another Expert Panel member for review.

D.3.2 Expert Panel review: Phases

The work of the Expert Panel was conducted in three phases.

Phase 1: Initial review

The aim of this phase was to categorise all research projects and to identify those where further detailed review was required to determine whether they were in scope. Information considered included the project title, project synopsis, key words and other project-level data. During this phase, information about projects was reviewed by one Expert Panel member. If the member was unable to make a determination, the project was referred for review by another member or additional information was provided for review by two members as part of Phase 2. At the end of this phase, projects were determined to be:

- out of scope for this review
- potentially in scope for this review, with detailed review to confirm determination
- recommended for detailed review, with additional information required before a determination could be made.

Phase 2: Detailed review

The aim of this phase was to conduct detailed review of research projects as recommended following Phase 1 to identify those that were in scope. As 'gain of function' is not a standard key-word term used in applications for funding or research publications, identification of relevant research required consideration of additional information such as detailed project plans, final reports to the funding agency and/or research outputs such as publications. During this phase, information about each research project was reviewed by two Expert Panel members. At the end of this phase, research projects were determined to be:

- out of scope for this review
- potentially in scope for this review (identified as in scope by at least one member of the Expert Panel).

Phase 3: Agreement on categorisation

The aim of this phase was for the Expert Panel to discuss all research projects identified by at least one member as potentially in scope for this review, and to reach agreement on the categorisation of the project. Disclosures of interest and management of any conflicts of interests were managed throughout the Expert Panel review process (see **Section D.1.3**). However, this aspect of the process was particularly critical during Phase 3 and was actively managed to ensure that Expert Panel members, observers and relevant NHMRC staff, including NHMRC's CEO, were not involved in the discussion or decision about a project with which they had any interest or involvement. At the end of this phase, research projects were determined to be:

- out of scope for this review
- in scope for this review.

Appendix E — Categorisation of research projects by Expert Panel

Criteria were developed in consultation with the Expert Panel to enable consistent categorisation of research projects by Expert Panel members (**Table 19**). These criteria were based on characteristics of an infectious agent which may increase its harmfulness to humans (see **Section 2.1.1**) and were developed to facilitate consistency of decision making by members. The application of the criteria was also reviewed regularly during Expert Panel meetings to ensure appropriateness and consistency of application.

Table 19. Categorisation of research projects by Expert Panel

#	Description	Details
1	Non-life sciences research and/or non-infectious disease research	Research that does not relate to life sciences and/or research that does not relate to infectious disease.
2	Life sciences research that does not involve any changes to the genome	Life sciences research that does not fit any of the definitions below, or is research into plants or infectious agents of plants. This is research that does not involve changes to the genome and does not involve any type of gain of function relevant to human or animal disease.
3	Research that involves changes to the genome using techniques that are not of concern and that does not fall into categories 4, 5 or 6	Research that may involve a technical gain of function, but the technique is not of concern. Examples include: • non-replicating viral vectors – e.g. lentivirus vectors, adenovirus vectors (e.g. AstraZeneca COVID-19 vaccine), Adeno-Associated Virus (AAV) vectors • insertion of a visual marker gene (e.g. GFP) for experimental purposes • insertion of an antibiotic resistance gene for experimental purposes (e.g. selection of a desired variant) that does not compromise standard treatment • live attenuated vaccines • use of standard laboratory strains of bacteria and fungi (e.g. *Escherichia coli* K12), as defined as hosts/vector systems for exempt dealings in Part 2, Schedule 2, Gene Technology Regulations 2001.
4	Gain-of-function research that involves infectious agents but is not of concern	Research involving infectious agents and gain of function that is not a technique described in category 3. Examples include: • addition of individual genetic changes or genes that may be associated with virulence, spread or evasion of vaccines, antivirals or antimicrobials, but where the final agent is expected to remain no more virulent than current strains • using a virion pseudotyping system to test receptor binding, or testing individual gene variants associated with virulence in a strain with multiple attenuations.

#	Description	Details
5	Gain-of-function research involving infectious agents that may harm humans, including but not limited to research involving infectious agents that may have pandemic potential (gain-of-function research of concern)	Creates a pathogen with significant potential for human harm by changes that lead to: • evasion of current vaccines • resistance to therapeutically useful antibiotics or antiviral agents • enhancement of virulence or making a non-pathogen virulent • increasing the transmissibility of a pathogen • altering the host range of a pathogen, such that it is more dangerous for humans • evasion of diagnosis and/or detection by established methods • increasing the ease by which an infectious agent might be weaponised.
6	Other research of concern (i.e. not gain-of-function research but has the potential to harm humans)	Examples include: • any work with prions or PC4 agents • culture of new agents or strains from environmental sources where there is an expectation that humans might be a host • attempts to recover/revive past pathogens.
7	Cannot determine	This option to be selected if the Expert Panel member was unable to make a determination, with reasons provided (e.g. insufficient information provided about the project).

Appendix F — Comparison of international biosafety guidelines

The information in this appendix compares biosafety guidance produced by the United States of America (USA) and those produced by Canada (CA), World Health Organization (WHO), Great Britain (GB), European Union (EU), Australia/New Zealand (AU/NZ) and Singapore (SG).[103] It should be noted that biosafety levels (BSL) are equivalent to physical containment levels (PC) in Australia.

Table 20. Comparison of International BSL-3 Requirements/Recommendations Regarding Standard Microbiological Practices[103]

NOTES:

1. While only the WHO Laboratory Biosafety Manual stipulates that access control must be enforced, this measure is routinely trained and adhered to as part of biosecurity awareness in Canada, England, Germany, Australia and Singapore.
2. Standards refer to use of 'Good Microbiological Techniques'; these are universally recognised as GMT.
3. Many countries' biosafety manuals and training programs discuss safe practices and disposal of sharps.
4. Many countries' biosafety manuals and training programs highlight the importance of communicating how a person's health status may predispose him or her to infection or, if pregnant, involve risk to the fetus. In Singapore and Hong Kong, pregnant women are often provided an option to work outside the BSL-3 to reduce the risk to the mother and fetus in the event of an accidental exposure (Barbara Johnson, personal observation, July 2015).

USA *BMBL* (BSL-3 Standard Microbiological Practices)	CA	WHO	GB	EU	AU/NZ	SG
The laboratory supervisor must enforce the institutional policies that control access to the laboratory.	1	✓	1	1	1	1
Persons must wash their hands after working with potentially hazardous materials and before leaving the laboratory.	–	✓	✓	–	✓	✓
Eating, drinking, smoking, handling contact lenses, applying cosmetics, and storing food for human consumption must not be permitted in laboratory areas.	✓	✓	✓	✓	✓	✓
Food must be stored outside the laboratory area in cabinets or refrigerators designated and used for this purpose.	2	✓	2	2	✓	✓
Mouth pipetting is prohibited; mechanical pipetting devices must be used.	✓	✓	2	–	✓	✓
Policies for the safe handling of sharps, such as needles, scalpels, pipettes, and broken glassware, must be developed and implemented.	✓	3	✓	3	✓	3
Whenever practical, laboratory supervisors should adopt improved engineering and work practice controls that reduce risk of sharps injuries.	✓	3	✓	3	3	3

USA *BMBL* (BSL-3 Standard Microbiological Practices)	CA	WHO	GB	EU	AU/ NZ	SG
Careful management of needles and other sharps are of primary importance. Needles must not be bent, sheared, broken, recapped, removed from disposable syringes, or otherwise manipulated by hand before disposal.	✓	✓	3	3	✓	3
Used disposable needles and syringes must be carefully placed in conveniently located puncture-resistant containers used for sharps disposal.	✓	✓	✓	–	✓	✓
Non-disposable sharps must be placed in a hard-walled container for transport to a processing area for decontamination, preferably by autoclaving.	✓	✓	✓	–	✓	✓
Broken glassware must not be handled directly. Instead, it must be removed using a brush and dustpan, tongs, or forceps.	3	✓	3	3	✓	✓
Plasticware should be substituted for glassware whenever possible.	–	✓	–	–	✓	–
Perform all procedures to minimise the creation of splashes and/or aerosols.	–	✓	✓	–	✓	✓
Decontaminate work surfaces after completion of work and after any spill or splash of potentially infectious material with appropriate disinfectant.	✓	✓	✓	–	✓	✓
Decontaminate all cultures, stocks, and other potentially infectious materials before disposal using an effective method.	✓	✓	✓	–	✓	✓
A method for decontaminating all laboratory wastes should be available in the facility, preferably within the laboratory (e.g. autoclave, chemical disinfection, incineration, or other validated decontamination method).	✓	✓	✓	✓	✓	✓
Depending on where the decontamination will be performed, the following methods should be used prior to transport: materials to be decontaminated outside of the immediate laboratory must be placed in a durable, leakproof container and secured for transport.	✓	✓	✓	–	✓	✓
A sign incorporating the universal biohazard symbol must be posted at the entrance to the laboratory when infectious agents are present.	✓	✓	✓	✓	✓	✓
Posted information must include the laboratory's biosafety level, the supervisor's name (or other responsible personnel), telephone number, and required procedures for entering and exiting the laboratory.	✓	✓	–	–	✓	✓
Agent information should be posted in accordance with the institutional policy.	–	✓	✓	–	✓	✓
An effective integrated pest management program is required.	✓	✓	✓	✓	✓	✓

USA *BMBL* (BSL-3 Standard Microbiological Practices)	CA	WHO	GB	EU	AU/NZ	SG
The laboratory supervisor must ensure that laboratory personnel receive appropriate training regarding their duties, the necessary precautions to prevent exposures, and exposure evaluation procedures.	✓	✓	✓	✓	✓	✓
Personnel must receive annual updates or additional training when procedural or policy changes occur.	✓	✓	✓	✓	✓	✓
Personal health status may affect an individual's susceptibility to infection and ability to receive immunisations or prophylactic interventions. Therefore, all laboratory personnel and particularly women of child-bearing age should be provided with information regarding immune competence and conditions that may predispose them to infection.	4	✓	4	4	✓	4
Individuals having these conditions should be encouraged to self-identify to the institution's health care provider for appropriate counselling and guidance.	4	4	4	4	✓	4

Table 21. Comparison of International BSL-3 Requirements/Recommendations Regarding BSL-3 Special Microbiological Practices[103]

USA *BMBL* BSL-3 Special Microbiological Practices	CA	WHO	GB	EU	AU/NZ	SG
All persons entering the laboratory must be advised of the potential hazards and meet specific entry/exit requirements.	✓		✓	✓	✓	✓
Laboratory personnel must be provided medical surveillance and offered appropriate immunisations for agents handled or potentially present in the laboratory.	✓	✓	✓	✓	✓	✓
Each institution should consider the need for collection and storage of serum samples from at-risk personnel.	–	–	–	–	✓	–
A laboratory-specific biosafety manual must be prepared and adopted as policy.	✓	✓	✓	–	✓	✓
The biosafety manual must be available and accessible.	✓	✓	✓	–		✓
The laboratory supervisor must ensure that laboratory personnel demonstrate proficiency in standard and special microbiological practices before working with BSL-3 agents.	✓	–	✓	–	✓	✓
Potentially infectious materials must be placed in a durable, leakproof container during collection, handling, processing, storage, or transport within a facility.	✓	–	✓	–	✓	✓
Laboratory equipment should be routinely decontaminated, as well as after spills, splashes, or other potential contamination.	✓	–	✓	–	✓	✓

USA *BMBL* BSL-3 Special Microbiological Practices	CA	WHO	GB	EU	AU/NZ	SG
Spills involving infectious materials must be contained, decontaminated, and cleaned up by staff properly trained and equipped to work with infectious material.	–	–	✓	–	✓	✓
Equipment must be decontaminated before repair, maintenance, or removal from the laboratory.	✓	–	✓	–	✓	–
Incidents that may result in exposure to infectious materials must be immediately evaluated and treated according to procedures described in the laboratory biosafety manual.	✓	–	✓	✓	✓	✓
All such incidents must be reported to the laboratory supervisor.	✓	✓	–	✓	✓	✓
Medical evaluation, surveillance, and treatment should be provided and appropriate records maintained.	–	✓	✓	✓	✓	✓
Animals and plants not associated with the work being performed must not be permitted in the laboratory.	–	✓	–	–	–	–
All procedures involving the manipulation of infectious materials must be conducted within a BSC or other physical containment devices.	✓	✓	✓	✓	✓	✓
No work with open vessels is conducted on the bench.	✓	✓	–	–	✓	✓
When a procedure cannot be performed within a BSC, a combination of personal protective equipment and other containment devices, such as a centrifuge safety cup or sealed rotor, must be used.	✓	✓	–	–	✓	✓

Table 22. Comparison of International BSL-3 Requirements/Recommendations Regarding BSL-3 Safety Equipment[103]

Note 1: Many countries have moved toward the use of nitrile gloves as they are more durable than latex and have moved away from latex because of allergic reactions.

USA *BMBL* BSL-3 Safety Equipment	CA	WHO	GB	EU	AU/NZ	SG
All procedures involving the manipulation of infectious materials must be conducted within a BSC (preferably Class II or Class III) or other physical containment devices.	✓	✓	✓	–	✓	✓
Workers in the laboratory wear protective laboratory clothing with a solid front, such as tie-back or wrap-around gowns, scrub suits, or coveralls.	✓	✓	✓	–	✓	✓
Protective clothing is not worn outside of the laboratory.	✓	✓	✓	✓	✓	✓
Reusable clothing is decontaminated with appropriate disinfectant before being laundered.	✓	✓	✓	✓	✓	–
Clothing is changed when contaminated.	–	–	✓	✓	–	–

USA *BMBL* BSL-3 Safety Equipment	CA	WHO	GB	EU	AU/ NZ	SG
Eye and face protection (goggles, mask, face shield, or other splatter guard) is used for anticipated splashes or sprays of infectious or other hazardous materials.	✓	✓	✓	–	✓	✓
Eye and face protection must be disposed of with other contaminated laboratory waste or decontaminated before reuse.	✓	–	✓	–	✓	–
Persons who wear contact lenses in laboratories must also wear eye protection.	–	–	–	–	–	–
Gloves must be worn to protect hands from exposure to hazardous materials.	✓	✓	✓	–	✓	✓
Glove selection should be based on an appropriate risk assessment.	1	✓	✓	1	–	1
Alternatives to latex gloves should be available.	1	1	1	1	–	1
Gloves must not be worn outside the laboratory.	–	✓	✓	–	✓	✓
Workers should change gloves when contaminated, integrity has been compromised, or when otherwise necessary.	–	–	–	–	–	–
Workers should wear 2 pairs of gloves when appropriate.	✓	✓	–	–	–	✓
Workers should remove gloves and wash hands when work with hazardous materials has been completed and before leaving the laboratory.	–	✓	✓	–	✓	✓
Workers should not wash or reuse disposable gloves.	–	–	–	–	–	–
Workers should dispose of used gloves with other contaminated laboratory waste.	–	–	✓	–	✓	–
Handwashing protocols must be rigorously followed.	✓	–	✓	–	–	✓
Eye, face, and respiratory protection must be used in rooms containing infected animals.	–	✓	–	–	✓	–

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