Risk Management Plan Australian Specific Annex	
Drug Substance	ChAdOx1-S (recombinant) (AZD1222)
EU RMP Version Number	1.0 Succession 5
Australian Specific Annex Version Number	1.0 Succession 4
Date	Date of final sign off

Australian Specific Annex to the EU Risk Management Plan for COVID-19 Vaccine AstraZeneca

ChAdOx1-S [RECOMBINANT]

Plan Approved by:

[redacted]

I approve this document
04 February 2021 | 20:16 AST

Senior Medical Director

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PRODUCT DETAILS

Active ingredient(s)	AZD1222
Product name(s):	COVID-19 Vaccine AstraZeneca[a]
Sponsor name:	AstraZeneca Pty Ltd
ASA version:	1.0 Succession 4
ASA version date:	Date of final sign off
Related EU RMP version:	1.0 Succession 5, dated 28 January 2021 (data lock 04 November 2020) Approved
Pharmaco-therapeutic group (ATC Code):	Covid-19 vaccines (J07BX03)
Pharmaceutical form(s) and strengths	Solution for injection. One dose (0.5 mL) contains COVID-19 Vaccine (ChAdOx1-S) 5×10^{10} viral particles.

[a]COVID-19 Vaccine AstraZeneca will be referred to by its development number (AZD1222) throughout this addendum

1. PRODUCT OVERVIEW

1.1 History of RMPs submitted in Australia

This is the fourth succession of the Australian Specific Annex (ASA) submitted for AZD1222 in Australia, to support a new biological entity registration via the provisional approval pathway. This ASA is an addendum to the approved EU RMP Version 1.0 Succession 5, dated 28 January 2021 which includes a description of the risk management system based on all information AstraZeneca deems relevant to the safety profile of AZD1222.

A summary of significant changes of the ASA over time is presented in Appendix 1.

This ASA has been updated to include the following:

Table 3: Addition of routine risk minimisation activities for the safety concern of ‘Use in elderly (>65 years of age).

Inclusion of information relating to a potential new safety risk within this plan should not be taken to imply that causal association with the use of AZD1222 has been established.

An interim Australian Biological Name (ABN; ‘ChAdOx1-S’) for AZD1222 was granted by the TGA. The final ABN will be confirmed during evaluation.

2. SAFETY SPECIFICATION

2.1 Epidemiology of the indication(s) and target population(s)

Coronavirus disease 19 (COVID-19) is a disease caused by the novel Coronavirus SARS-CoV-2 and is a major health threat and international crisis caused by a virus not previously seen in humans. It is also highly infectious, can affect people severely and has led to a worldwide pandemic (1). COVID-19 is predominantly a disease of the respiratory system, particularly in the early stages of the illness and can cause acute respiratory illness. Common early symptoms are similar to other respiratory illnesses and include fever, cough, sore throat, runny nose and shortness of breath. In some people infection can progress to become a more severe disease, with the immune system overreacting, resulting in inflammation and lack of oxygen to many parts of the body which can lead to multiple organ failure and death (1).

Incidence and Prevalence of COVID-19 in Australia

Australia's first case was diagnosed on 25 January 2020 (1). As at 06 December 2020, there were 28, 049 COVID-19 cases reported nationally in Australia with two distinct peaks of outbreaks occurring in March and July 2020 (2, 3). The second peak began in early July, corresponding with community transmission in Victoria and since then there has been an overall downward trend in cases (3).

Nationally, since the beginning of the epidemic, there have been 830 outbreaks in Australia associated with 13,238 cases. Outbreaks were reported most frequently from residential aged care settings, workplaces, ships, and family and social gatherings (3).

At the start of the epidemic a substantial number of infections were acquired overseas (1). To date, the infection rate for all locally-acquired cases was highest in Victoria with 293.6 infections per 100,000 population (3).

Some states and territories have experienced higher numbers and more substantial community-associated transmission. These differences arise from factors including state demographics, population size, and patterns of overseas arrivals. Australia continues to experience low levels of community transmission of COVID-19 in some jurisdictions (3).

COVID-19 in Sub-Populations

People aged ≥ 90 years old continue to have the highest infection rate overall. This trend is likely to reflect the large number of outbreaks that occurred in aged care settings, which has declined more recently. Other demographic trends remained consistent, with children aged 0–9 years old having the lowest rate of infection, and cases in Aboriginal and Torres Strait Islander persons accounting for fewer than 1% of all confirmed cases (3).

There has been similar infection rates in males and females with the ratio being approximately 1:1 in most age groups, except in the 20-29 years age group and those aged ≥ 80 years old where rates were higher among females and in the 70-79 years age group where rates were higher in males (3).

Since the beginning of the epidemic in Australia, the median age of all cases was 37 years old and this has not changed since the beginning of August 2020. Prior to 1 June 2020, COVID-19 cases were slightly older with a median age of 46 years old and a high proportion of cases having had a recent overseas travel history or acquisition on a cruise ship. In cases reported after 1 June 2020, the median age was 34 years old reflecting transmission in the community and across a range of settings, especially in Victoria (3).

As at 06 December 2020, there were 4,298 cases of COVID-19 associated with 219 residential aged care facilities, with 3,613 recoveries and 685 deaths. 2,049 of these cases occurred in aged care residents, with the remaining 2,294 cases occurring in care staff (3).

There have been 147 cases of COVID-19 notified in Aboriginal and Torres Strait Islander persons since the beginning of the epidemic. This represents approximately 0.5% of all confirmed cases (3). The median age of COVID-19 cases in Aboriginal and Torres Strait Islander persons was 31 years old, which was younger than for Non-Indigenous cases where the median age was 37 years old (3).

The notification rate across all age groups was higher in Non-Indigenous persons than in Aboriginal and Torres Strait Islander persons (3). Amongst Aboriginal and Torres Strait Islander cases, the highest notification rate was in those aged 70–79 years and similar to Non-Indigenous cases, children aged 0–9 years had the lowest notification rate among Aboriginal and Torres Strait Islander cases. (3).

Risk Factors for COVID-19

Population groups who are most at risk of exposure to COVID-19 or developing severe illness include: health care workers, Aboriginal and Torres Strait Islander groups, older people (70 years of age and older), people living in aged care facilities, people with chronic conditions and comorbidities and people with disability (1,4). Risk also rises with age, being male, poverty, smoking and being obese BMI ≥ 40kg/m^2 (5).

People with chronic conditions and comorbidities who are most at risk include chronic renal failure, chronic heart disease, chronic lung disease, cancer, diabetes, chronic liver disease, some neurological conditions (e.g. stroke, dementia), chronic inflammatory conditions, hypertension, transplant recipients, patients with compromised immune systems, patients on immunosuppressive therapy and patients having chemotherapy or radiotherapy (5).

Residents of aged care facilities are at increased risk of COVID-19 infection due to the environment of communal living facilities and due to factors such as their age, chronic conditions and comorbidities they are more vulnerable to serious complications if they do become infected (3). People who live in shared residential settings, such as correctional facilities, military bases, and residential disability care facilities are also at increased risk of infection from outbreaks in these settings (1). Other particular groups at risk were those who returned from overseas, had been on cruise ships or lived with a person who had caught the virus overseas (1).

Morbidity and Mortality

Reported hospitalisation rates for COVID-19 positive cases in Australia were approximately 12% (3) and ICU admission rates amongst hospitalized patients in Australia were approximately 20%. Australia reports a median length-of-stay of 7.0 days for surviving hospitalised patients (4).

In Australian hospitalised patients, the most prevalent comorbidity was cardiac disease (36%); diabetes was common across hospitalized patients and particularly amongst those who died while in hospital (43%). Over a quarter of ICU-admitted COVID-19 patients were classified as obese (a body mass index of > 30 or over 120 kg) (4).

Amongst those admitted to ICU, mortality rates increased with rising numbers of comorbidities. The highest case fatality rate (CFR) of all comorbidities was for those with a malignancy (46%) followed by those with chronic renal disease (40%). A history of smoking, was identified where data were available in 34% of those hospitalised and 13% of those admitted to an ICU. Only five of the hospitalised cohort were pregnant at the time of their hospitalisation (1.2%) (3).

As at 06 December 2020, there were 908 deaths reported nationally due to COVID-19 (2) and a high proportion of these deaths (685 as at 06 December 2020) were associated with residential aged care facilities (3). The majority were in the older age groups, with the 80–89 age group having the most deaths. There are steep increases in death rates across the age groups and higher rates for males than females, particularly in the oldest age groups. (1). The median age at death for COVID-19 in Australia was 80 years (1). The overall mortality rate among hospitalised cases and among adults admitted to ICU is substantially lower than observed in overseas cases (3).

Main Treatment Options

There is currently no immunity in the population and currently no vaccine or specific antiviral treatments for COVID-19 in Australia. Antiretrovirals such as remdesivir (Veklury) have been temporarily approved by the TGA for very sick patients. Corticosteroids such as

dexamethasone are being used to reduce inflammation. The majority of patients with mild disease are managed in the community with symptomatic treatment. Patients with severe disease will require hospitalization where treatment is aimed at supportive medical care including supplemental oxygen and mechanical ventilatory support when indicated (6).

2.2 Summary of the safety concerns

The safety concerns for AZD1222 are presented in Table 3. Since the previous ASA Version 1 Succession 3, dated 30 January 2021, there have been no changes to the list of safety concerns.

2.2.1 Australian-specific safety concerns

As recommended by the TGA during evaluation (PM-2020-06115-1-2) for ASA Version 1 Succession 1, dated 22 December 2020, 'Use in elderly (>65 years of age)' is added as missing information.

Risks Considered Important for Inclusion in the List of Safety Concerns

Use in elderly (>65 years of age)

Risk benefit impact

This population is potentially at risk of developing a more severe manifestation of COVID-19. Safety of AZD1222 was generally similar in older adults compared with younger adults 18 to 64 years of age, with older adults reporting reduced reactogenicity. There were no clinically meaningful imbalances in the incidence of SAEs or AESIs between the AZD1222 and control groups in this age group. There is no evidence that the safety profile of this population receiving AZD1222 will be different to that of the general population. As persons ≥ 65 years of age have been identified as a priority group for initial vaccination in several jurisdictions following vaccine availability, continuing to collect safety data in this population receiving AZD1222 is important.

Presentation of Missing Information

Evidence source

This population is potentially at risk of developing a more severe manifestation of COVID-19. There is no evidence that the safety profile of this population receiving AZD1222 will be different to that of the general population.

Population in need of further characterisation

Use in elderly (>65 years of age) continues to be evaluated through ongoing clinical studies (in the AZD1222 clinical development programme) and this population will be included in the planned pharmacovigilance activities (Enhanced Active Surveillance, a post-marketing observational study using existing secondary health data sources).

3. PHARMACOVIGILANCE PLAN

3.1 Routine pharmacovigilance activities in Australia.

Routine PV activities outlined in Section III.1 of the EU RMP Version 1.0 Succession 5, dated 28 January 2021 are considered relevant to Australia.

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection include the following:

3.1.1 Specific Adverse Reaction Follow-Up Questionnaires

Targeted AE follow-up questionnaires will be used to collect further information on important potential risks. Refer to Annex 4 of the EU RMP Version 1, Succession 5 dated 28 January 2021.

As recommended by the TGA during evaluation (PM-2020-06115-1-2) for ASA Version 1 Succession 1, dated 22 December 2020, “Myocardial infarction” has been added as an adverse event of special interest in response to TGA’s request to address cardiac related Adverse Events of Special Interest (AESIs).

Refer to Section II.7.1.3 and Annex 7 of the EU RMP Version 1, Succession 5, dated 28 January 2021 for the list of AESIs.

There are no Australian-specific AESIs.

The AstraZeneca standard follow-up form, which is provided to the reporter together with the applicable targeted AE follow-up questionnaire, includes a field for ethnicity.

3.1.2 Monthly Safety Summary Reports

Monthly Safety Summary Reports as described in Section III.1.4 of the EU RMP Version 1 Succession 5, dated 28 January 2021 will be provided to the TGA. Continuation of the monthly safety summary reports will be evaluated at the time of the first PBRER.

As recommended by the TGA during evaluation (PM-2020-06115-1-2; RMP RFI set #2) for ASA Version 1 Succession 1, dated 22 December 2020, the Monthly Safety Summary Reports will include the following information:

- Interval and cumulative number of reports, stratified by report type (medically confirmed/not) and by seriousness (including fatal separately)
- Interval and cumulative number of reports (serious and non-serious), overall and by age groups and in special populations (e.g. pregnant women)
- Interval and cumulative number of reports per HLT and SOC
- Number of reports in Australia and Global
- Exposure data, stratified by country, age groups, race and ethnicity, where information is available
- Changes to the reference safety information (Core Data Sheet) in the interval
- Validated signals associated with designated medical events will be included.
- Ongoing and closed signals in the interval
- Reports on number and relevant cases, including time-to-onset and Observed/Expected analyses for the list of AESI and RMP safety concerns
- Fatal reports – numbers and relevant cases. Observed/expected analyses will be conducted for the AESI of Sudden Death.
- Number and relevant cases for Vaccination errors will be included. Potential interaction with other vaccines/concomitant treatments and Vaccination failure / lack of efficacy (including confirmed and suspected cases) will be presented in the PBRER.
- Summary of any outcomes of routine pharmacovigilance activities (as presented in the EU RMP Part III and applied in the Australian context) that have a potential impact on the benefit/risk balance of the vaccine should be included for the purpose of rapid signal detection and communication activities.
- Risk/benefit considerations

3.1.3 Traceability

To facilitate pharmacovigilance and batch/lot analysis every effort will be made to support the recording and accessibility of brand and batch/lot numbers for HCPs and patients in Australia.

The Australian Government Department of Health will implement a plan to include the vaccine name and batch information in every recipient's immunisation record (Australian Immunisation Register). The draft plan is presented in Appendix 2. In addition, the Australian Government Department of Health will consider the implementation of patient Vaccination cards.

As a consequence, the description in EU RMP Section III.1 for how batch/lot numbers will be traced in Europe is not applicable in Australia.

Post marketing individual case reports for AZD1222 without an associated batch number will be systemically followed up. AstraZeneca standard follow up forms include a field for the batch number. Batch information will be included in the global safety database.

3.2 Additional Pharmacovigilance activities

The ongoing and planned additional PV activities (including EU, UK, US, Japan) outlined in Section III.2, of the EU RMP Version 1.0 Succession 5, dated 28 January 2021 are relevant to Australia. This includes two new planned studies to address the safety concern of 'Use in immunocompromised patients'. Refer to Table 1.

Although there are no planned Australian subjects, consideration will be given for inclusion of Australian subjects in the AZD1222 Pregnancy Registry.

Table 1 presents a summary of ongoing and planned additional PV activities. As per EU RMP Version 1.0 Succession 5, dated 28 January 2021, ongoing clinical studies (COV001, COV002, COV003, COV004, COV005, D8110C00001 and D8111C00002) are now included.

There are no Australian specific additional PV activities.

Refer to Annex 3 of the EU RMP Version 1, Succession 5, dated 28 January 2021 for draft protocols.

Table 1 Ongoing and planned additional pharmacovigilance activities

Study	Objectives	Safety Concerns addressed	Milestones
Ongoing			
Study COV001 A Phase I/II Study to Determine Efficacy, Safety, and Immunogenicity of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 nCoV-19 in UK Healthy Adult Volunteers	Primary Objectives: To assess efficacy of AZD1222 against COVID-19 To assess the safety of AZD1222 Key secondary Objectives: To assess the reactogenicity profile of AZD1222 To assess cellular and humoral immunogenicity of AZD1222	Nervous system disorders, including immune-mediated neurological conditions, Vaccine-associated enhanced disease (VAED), including vaccine associated enhanced respiratory disease (VAERD), Anaphylaxis, Long-term safety	Final study report due Q1 2022
Study COV002 A Phase II/III Study to Determine the Efficacy, Safety, and Immunogenicity of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 nCoV-19	Primary Objectives: To assess efficacy and safety of AZD1222 against COVID-19 in adults aged 18 years and older in the UK Secondary Objectives: To assess the reactogenicity profile of AZD1222 To assess efficacy of AZD1222 against severe and non-severe COVID-19 To assess humoral immunogenicity of AZD1222 To assess cellular immunity of AZD1222 in older adults To assess the safety and immunogenicity of a booster dose of AZD1222 in older adults aged 56 years or older (two-dose schedule).	Nervous system disorders, including immune-mediated neurological conditions, Vaccine-associated enhanced disease (VAED), including vaccine associated enhanced respiratory disease (VAERD), Anaphylaxis, Long-term safety, Use in elderly (>65 years of age)	Final study report due Q2 2022
Study COV003 A Randomised, Controlled, Phase III Study to Determine the Safety, Efficacy, and Immunogenicity of the Non-Replicating ChAdOx1 nCoV-19 Vaccine	Primary Objective: To evaluate the efficacy of AZD1222 vaccine against COVID-19 disease confirmed with PCR Secondary Objectives: To evaluate the safety, tolerability and reactogenicity profile of AZD1222 To evaluate the efficacy of AZD1222 against severe and non-severe COVID-19 disease To evaluate the humoral immunogenicity of AZD1222 To assess the cellular immunogenicity of AZD1222.	Nervous system disorders, including immune-mediated neurological conditions, Vaccine-associated enhanced disease (VAED), including vaccine associated enhanced respiratory disease (VAERD), Anaphylaxis, Long-term safety, Use in elderly (>65 years of age)	Final study report due Q2 2022

Study COV004 A Phase IB/II Single- Blinded, Randomised, Controlled Study to Determine Safety, Immunogenicity and Efficacy of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 nCoV-19 in Adults in Kenya	Primary Objectives: To assess the safety, tolerability and reactogenicity profile of the candidate vaccine ChAdOx1 nCoV-19 To assess immunogenicity of ChAdOx1 nCoV-19 Secondary Objectives: To assess humoral immunogenicity of ChAdOx1 nCoV-19 at early and late timepoints To assess cellular immunogenicity of ChAdOx1 nCoV-19 To assess efficacy of ChAdOx1 nCoV-19 against COVID-19	Nervous system disorders, including immune-mediated neurological conditions, Vaccine-associated enhanced disease (VAED), including vaccine associated enhanced respiratory disease (VAERD), Anaphylaxis, Long-term safety	Final study report due 2022
Study COV005 An Adaptive Phase I/II Randomised Placebo-controlled Trial to Determine Safety, Immunogenicity and Efficacy of Non- Replicating ChAdOx1 SARS-CoV-2 Vaccine in South African Adults Living Without HIV, and Safety and Immunogenicity in Adults living with HIV.	Primary Objective: To assess the safety of AZD1222 in healthy HIV-uninfected adults To assess efficacy of AZD1222 against COVID-19 To assess the safety of the candidate vaccine AZD1222 in adults living with HIV To evaluate the immunogenicity of AZD1222 after first and second doses of vaccine in adults living with HIV Secondary Objectives: To assess the immunogenicity of AZD1222 in healthy HIV-uninfected adults.	Nervous system disorders, including immune-mediated neurological conditions, Use in immunocompromised patients, Vaccine-associated enhanced disease (VAED), including vaccine associated enhanced respiratory disease (VAERD), Anaphylaxis, Long-term safety	Final study report due: Q2 2022
D8110C00001 A Phase III Randomized, Doubleblind, Placebocontrolled Multicentre Study in Adults to Determine the Safety, Efficacy, and Immunogenicity of AZD1222, a Nonreplicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19	Primary Objectives: To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19 in adults ≥ 18 years of age To assess the safety and tolerability of 2 IM doses of AZD1222 compared to placebo in adults ≥ 18 years of age To assess the reactogenicity of 2 IM doses of AZD1222 compared to placebo in adults ≥ 18 years of age (Substudy only) Key Secondary Objectives: To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of SARS-CoV-2 infection To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of symptomatic COVID-19 using CDC criteria	Nervous system disorders, including immune-mediated neurological conditions, Vaccine-associated enhanced disease (VAED), including vaccine associated enhanced respiratory disease (VAERD), Anaphylaxis, Long-term safety, Use in elderly (>65 years of age)	Interim analysis due: Q1 2021

	To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of University of Oxford-defined symptomatic COVID-19 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo in the prevention of COVID-19 in all study participants, regardless of evidence of prior SARS-CoV-2 infection To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of severe or critical symptomatic COVID-19 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19-related Emergency Department visits		
D8111C00002 A Phase I/II Randomized, Doubleblind, Placebocontrolled Multicentre Study in Participants Aged 18 Years or Older to Determine the Safety and Immunogenicity of AZD1222, a Nonreplicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19	Primary Objectives: To assess antibody responses to AZD1222 Spike antigen following 2 IM doses of AZD1222 or placebo. To assess the safety, tolerability, and reactogenicity profile of the candidate vaccine AZD1222. Secondary Objectives: To assess antibody responses to AZD1222 RBD antigen following 2 IM doses of AZD1222 or placebo. To assess time course of antibody to AZD1222 Spike and RBD antigens of AZD1222 (MSD serology assay) To assess the function of nAb against SARS-CoV-2 spike protein To assess the safety of the candidate vaccine AZD1222. To describe occurrence of symptomatic COVID-19 in recipients of AZD1222 and placebo. To describe occurrence of severe COVID- 19 and seroresponse to non-Spike SARSCoV-2 antigens.	Nervous system disorders, including immune-mediated neurological conditions, Vaccine-associated enhanced disease (VAED), including vaccine associated enhanced respiratory disease (VAERD), Anaphylaxis, Long-term safety, Use in elderly (>65 years of age)	Interim analysis due Q12021 Primary analysis due Q2021
Planned			
Enhanced Active Surveillance Study A Phase IV Enhanced Active Surveillance Study of People	Primary Objectives: To assess the safety and tolerability of at least 1 IM dose of AZD1222 in adults ≥ 18 years of age for 3 months after vaccination with the first dose of AZD1222. Secondary Objectives:	Nervous system disorders, including immune-mediated neurological conditions, Vaccine-associated enhanced	Final study protocol available: 23 February 2021 Start of study: 18 May 2021 First interim report available: Q3 2021

Vaccinated with AZD1222 D8111R00003 (EU) D8110R00001 (US) ESR 21-21121 (UK, DSRU sponsored)	To assess the longer-term safety and tolerability of at least 1 IM dose of AZD1222 for 18 months after vaccination. To assess the safety and tolerability of AZD1222 in participants ≥ 65 year of age and in other key subgroups. To estimate the frequency of select pregnancy outcomes in women vaccinated with AZD1222 during pregnancy or within 45 days of the estimated conception date. To estimate the frequency of select outcomes in neonates/infants born to mothers vaccinated with AZD1222 during pregnancy or within 45 days of the estimated date of conception.	disease (VAED), including vaccine associated enhanced respiratory disease (VAERD), Anaphylaxis, Use during pregnancy and while breastfeeding, Use in immunocompromised patients, Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders), Use in patients with autoimmune or inflammatory disorders, Interactions with other vaccines, Long-term safety, Use in elderly (>65 years of age)	
AZD1222 Pregnancy Registry: Pregnancy Registry of Women Exposed to AZD1222 Immediately Before or During Pregnancy as Part of the C-VIPER Registry Consortium ESR-21-21138 (Pregistry-externally sponsored)	Primary Objectives: To estimate the frequency of selected adverse pregnancy outcomes (ie, spontaneous abortions, stillbirths, and preterm births) in women receiving at least 1 dose of the AZD1222 vaccine during pregnancy or up to a predefined period (eg 30 days) before estimated date of last menstrual period (LMP). To estimate the risk of selected adverse foetal/neonatal outcomes (ie, major congenital malformations and small for gestational age) at birth and up to at least the 12 months of life (to account for diagnosis of major congenital malformations that might be delayed) in infants from pregnancies in which the mothers received the AZD1222 vaccine during pregnancy or up to a predefined period (eg, 30 days) before estimated date of LMP.	Use during pregnancy and while breastfeeding	Study protocol submitted to EMA on 27 January 2021
Post-marketing observational study using existing secondary health data sources A post-authorisation/ Post-marketing observational study using existing secondary health data sources to evaluate the association between exposure to AZD1222 and safety concerns.	Primary Objectives: To estimate the incidence of safety concerns and AESIs in recipients and non-recipients of AZD1222, among all populations targeted for vaccination and in the specific populations considered as missing information To estimate the relative risk (comparing exposed and unexposed person time) of safety concerns including adverse events of interest among all populations targeted for vaccination and in the specific populations considered as missing information	Nervous system disorders, including immune-mediated neurological conditions, Vaccine-associated enhanced disease (VAED), including vaccine associated enhanced respiratory disease (VAERD), Anaphylaxis, Use during pregnancy and while breastfeeding, Use in immunocompromised patients, Use in frail patients with co-morbidities (eg, chronic	Study protocol available by 01 April 2021

D8111R00006 (EU/UK) Study code to be confirmed (US)	To characterise the use of AZD1222 among all populations targeted for vaccination and in the specific populations considered as missing information.	obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders), Use in patients with autoimmune or inflammatory disorders, Interactions with other vaccines, Long-term safety, Use in elderly (>65 years of age)	
Post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency	To evaluate the safety profile of AZD1222 in patients receiving immunosuppressant medication(s) or with primary immunodeficiency	Use in immunocompromised patients	Study protocol expected 01 November 2021
Interventional study in immunocompromised subjects	Primary objective: To evaluate the safety profile of AZD1222 in patients receiving immunosuppressant medication(s) or with primary immunodeficiency	Use in immunocompromised patients	Study protocol due 28 February 2021
Post-marketing effectiveness study: Post-authorisation/ Post-marketing retrospective cohort study to evaluate the effectiveness of the AZD1222 vaccine to prevent serious COVID-19 infection in conditions of usual care through public private partnership with COVIDRIVE utilising primary data collected prospectively through the COVIDRIVE platform. D8111R00005 (EU/UK) Study code to be confirmed (US)	To estimate brand specific vaccine effectiveness against laboratory-confirmed SARS-CoV-2 in hospitalized patients, overall and by age group (< 18, 18-64 and ≥ 65 years old), after adjusting for potential confounders.	N/A	Study protocol expected March 2021 (COVIDRIVE consortium)

4. CLINICAL STUDY PLAN FOR PROVISIONAL REGISTRATION

The provisional approval clinical study plan for AZD1222 is summarised in Table 2.

Table 2 Provisional approval clinical study plan for AZD1222

Study Country Phase	Current status	Confirmatory nature (i.e. uncertainty addressed)	Test products, Dosage regimen [a]	Study population	Planned no. participants	N of vaccinated participants as of DEC 2020	Duration of follow-up	Data available for submission (estimate)
Pivotal studies (randomised, controlled, multicentre, blinded)								
COV001 UK Phase I/II (PB)	Start date APR20 Ongoing	Confirmatory final efficacy, safety & immunogenicity data in adults (18-55 years)	AZD1222: SD = 5 × 1010 vp LD = 2.5 × 1010 vp Control: MenACWY Single dose SD or C; SD/SD or C/C, 4-6 wks apart; SD/SD, C/C, or SD/LD, 8 wks apart	Healthy adults aged 18-55 years	Up to 1090	1067	364 days after the last dose	Final report due Q1 2022
COV002 UK Phase II/III (PB)	Start date MAY20 Ongoing	Confirmatory final efficacy, safety & immunogenicity data in adults & children (5 years & older) Age escalation inc. 5-12 years Single dose or 2 doses	AZD1222: SD = 5 × 1010 vp LD = 2.2 × 1010 vp b Control: MenACWY Single dose SD or C; SD/SD, SD/LD, or C/C, 4-6 wks apart; SD/SD, SD/LD, or C/C, ≥ 4 wks apart	Main efficacy study: adults aged ≥18 years. Priority given to health professionals & adults with high potential for exposure to SARS-CoV-2 Safety & immunogenicity sub-studies: • Healthy children aged 5-12 years • HIV+ adults aged 18-55 years	Up to 12 390	10 663	364 days after the last dose	Final report due Q2 2022

Study **Country** **Phase**	**Current status**	**Confirmatory nature (i.e. uncertainty addressed)**	**Test products, Dosage regimen** [a]	**Study population**	**Planned no. participants**	**N of vaccinated participants as of DEC 2020**	**Duration of follow-up**	**Data available for submission (estimate)**
COV003 Brazil Phase III (PB)	Start date JUN20 Ongoing	Confirmatory final efficacy, safety & immunogenicity data (18 years & older; high potential exposure to SARS-CoV-2)	AZD1222: SD = 5 × 1010 vp Control: MenACWY (1st dose) & saline (PBO) (2nd dose). Single dose SD or C; SD/SD or MenACWY/PBO, 4-12 wks apart	Adults aged ≥18 years, health professionals & adults with high potential for exposure to SARS-CoV-2	Up to 10 300	10 002	364 days after the last dose	Final report due Q2 2022
COV005 South Africa Phase III (DB)	Start date JUN20 Ongoing	Confirmatory final safety, efficacy & immunogenicity data (18-65 years with or with HIV infection)	AZD1222: SD = 5-7.5 × 1010 vp LD = 2.2 × 1010 vp b Control: Saline (PBO) LD/SD, SD/SD, or C/C, 4 wks apart	Adults aged 18-65 years, living with and without HIV	Up to 2070	2013	364 days after the last dose	Final report due Q2 2022
Supportive study (randomised, double-blind, placebo-controlled)								
D8110C00001 US, Chile, Peru Phase III (DB)	Start date AUG20 Ongoing	Confirmatory efficacy, safety & immunogenicity data in healthy adults or with medically stable chronic disease, high potential exposure to SARS-CoV-2 2 doses	AZD1222: SD = 5 × 1010 vp Control: Saline (PBO) SD/SD 4 wks apart	≥18 yr, healthy or with medically stable chronic disease	30 000	25 711	~730 days after first dose	Interim analysis report due Q1 2021

C control; DB double-blind; HIV human immunodeficiency virus; LD low dose; no number; MenACWY = meningococcal group a, c, w-135, and y conjugate vaccine; PB participant-blind; PBO placebo; SD standard dose; vp viral particles; wks weeks; yr years

[a] AZD1222 dose levels are approximations.

[b] Low dose was due to a potency miscalculation, and was administered to a subset of study participants.

5. RISK MINIMISATION PLAN

5.1 Routine risk minimisation activities

The Australian Product Information (PI) is the primary tool to communicate the benefits and risks associated with AZD1222 use. The routine risk minimisation activities in Australia and Europe for each listed safety concern are consistent.

Table 3 presents a summary of planned risk minimisation measures.

5.2 Additional risk minimisation activities

As for the EU RMP, there are no additional risk minimisation measures planned for Australia. Routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product.

5.3 How additional risk minimisation activities will be evaluated in Australia

No evaluation will be performed, as there are no additional risk minimisation activities to be undertaken for any of the safety concerns in Australia.

6. SUMMARY OF THE RMP

The safety concerns, pharmacovigilance plan and planned risk minimisation measures described in the EU RMP Version 1.0 Succession 5, dated 28 January 2021 are applicable to Australia. Please refer to Table 3 which gives a summary of the safety concerns for Australia, and the associated routine and additional activities relevant to Australia.

Table 3 Summary of pharmacovigilance and risk minimisation activities proposed for Australia

Safety Concerns or Missing Information	Risk minimisation activities (routine and additional) proposed for Australia (based on proposed PI and CMI	Pharmacovigilance activities (routine and additional) proposed for Australia
Important identified risks		
None		
Important Potential risks		
Nervous system disorders including immune-mediated neurological conditions	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire for immune-mediated neurological conditions only. Additional PV: Enhanced Active Surveillance, Post-marketing observational study using existing secondary health data sources Study COV001 Study COV002 Study COV003 Study COV004 Study COV005 Study D8110C00001 Study D8111C00002
Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional PV: Enhanced Active Surveillance, Post-marketing observational study using existing secondary health data sources Study COV001 Study COV002 Study COV003 Study COV004 Study COV005 Study D8110C00001 Study D8111C00002

Safety Concerns or Missing Information	Risk minimisation activities (routine and additional) proposed for Australia (based on proposed PI and CMI	Pharmacovigilance activities (routine and additional) proposed for Australia
Anaphylaxis	Routine risk communication: PI Section 4.3 and 4.4 CMI Section 2 Additional: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: Enhanced Active Surveillance Post-marketing observational study using existing secondary health data sources Study COV001 Study COV002 Study COV003 Study COV004 Study COV005 Study D8110C00001 Study D8111C00002
Missing information		
Use during pregnancy and while breastfeeding	Routine risk communication: PI Section 4.6 CMI Section 2 Additional: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional PV: Additional PV: Enhanced Active Surveillance Study, Post-marketing observational study using existing secondary health data sources, AZD1222 Pregnancy Registry.
Use in immunocompromised patients	Routine risk communication: PI Section 4.4 CMI Section 2 Additional: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional PV: Enhanced Active Surveillance, Post-marketing observational study using existing secondary health data sources Post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency Study COV005 Interventional study in immunocompromised patients

Safety Concerns or Missing Information	**Risk minimisation activities (routine and additional) proposed for Australia (based on proposed PI and CMI**	**Pharmacovigilance activities (routine and additional) proposed for Australia**
Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional PV: Enhanced Active Surveillance, Post-marketing observational study using existing secondary health data sources
Use in patients with autoimmune or inflammatory disorder	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Enhanced Active Surveillance Post-marketing observational study using existing secondary health data sources
Interactions with other vaccines	Routine risk communication: PI Sections 4.5 CMI Section 2 Additional: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional PV: Enhanced Active Surveillance Study, Post-marketing observational study using existing secondary health data sources
Long-term safety	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Enhanced Active Surveillance Post-marketing observational study using existing secondary health data sources Study COV001 Study COV002 Study COV003 Study COV004 Study COV005 Study D8110C00001 Study D8111C00002

Safety Concerns or Missing Information	**Risk minimisation activities (routine and additional) proposed for Australia (based on proposed PI and CMI**	**Pharmacovigilance activities (routine and additional) proposed for Australia**
Use in elderly (>65 years of age) (Recommended by the TGA)	Routine risk communication: PI Section 4.4 Additional: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Enhanced Active Surveillance, Post-marketing observational study using existing secondary health data sources Study COV002 Study COV003 Study D8110C00001 Study D8111C00002

7. PERSON RESPONSIBLE FOR THIS RMP AND CONTACT DETAILS

Table 4 RMP contact

Contact	Name	Email Address	Phone	Fax
Patient Safety – Primary Contact Patient Safety Manager	[redacted]			

8. REFERENCES

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6. Thevarajan I, Buising K and Cowie B. Clinical presentation and management of COVID-19. Med J Aust 2020; 213 (3): 134-139. || doi: 10.5694/mja2.50698
Published online: 3 August 2020

9. APPENDICES

Appendix 1 Summary of Major Changes Over Time

ASA Version	ASA Date	Parent RMP Version	Revision History
1.0 Succession 1	22 December 2020	EU RMP Version 1.0 Succession 1 Dated 21 December 2020	NA first ASA for COVID-19 Vaccine AstraZeneca
1.0 Succession 2	14 January 2021	EU RMP Version 1.0 Succession 1 Dated 21 December 2020	Per TGA recommendations (Submission number: PM-2020-06115-1-2) the following information has been added: Section 3.1: Submission of monthly summary reports; continuation of these reports will be evaluated at the time of the first PBRER. Section 3.1: Addition of myocardial infarction as an adverse event of special interest. Myocardial infarction AESI Preferred Terms (PTs) and AE follow-up questionnaire are presented in Appendix 2. Appendix 3: AstraZeneca's standard follow up forms Section 4 and Table 2: Proposed provisional approval clinical study plan

1.0 Succession 3	30 January 2021	EU RMP Version 1.0 Succession 4 Dated 26 January 2021	As recommended by the TGA during evaluation (PM-2020-06115-1-2) for ASA Version 1 Succession 1, dated 22 December 2020, this ASA has been updated to include the following: Section 2.2.1 and Table 3: 'Use in elderly (>65 years of age)' is added as missing information. Section 3.1.2: Key information for inclusion in the Monthly Summary Safety Reports The following information has been included in the EU RMP Version 1 Succession 4, dated 26 January 2021, this ASA has also been updated as a consequence. Section 2.2 and Table 3: The important potential risk of 'Immune-mediated neurological conditions' is updated to 'Nervous system disorders, including immune-mediated neurological conditions' The important potential risk of 'Vaccine-associated enhanced disease (VAED)' includes 'Vaccine-associated enhanced respiratory disease (VAERD)'. 'Anaphylaxis' is added as an important potential risk for AZD1222. The missing information of 'Use of AZD1222 in pregnant and breastfeeding women' is amended to 'Use during pregnancy and while breastfeeding'. The missing information of 'Use of AZD1222 in subjects with severe immunodeficiency or requiring immunosuppressive medications' is updated to 'Use in immunocompromised patients'. The missing information of 'Use of AZD1222 in subjects with severe and/or uncontrolled underlying disease' is updated to 'Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)'. The topics of 'Use in patients with autoimmune or inflammatory disorders' and 'Long-term safety' are added as missing information. The missing information topic of 'Use with other vaccines' is updated to 'Interactions with other vaccines' Section 3.2 and Tables 1 and 3: Additional planned pharmacovigilance studies to address the missing information of 'Use in immunocompromised patients' Table 1 includes ongoing clinical studies (COV001, COV002, COV003, COV004, COV005, D8110C00001 and D8111C00002.

ASA Version	ASA Date	Parent RMP Version	Revision History
			Appendix 4: Department of Health Draft Implementation Plan for Traceability. Appendices 2 and 3 removed.
1.0 Succession 4	Date of final sign off	EU RMP Version 1.0 Succession 5 Dated 28 January 2021	Table 3: addition of routine risk minimisation information for the missing information 'Use in elderly (>65 years of age)'.

Appendix 2 Department of Health Draft Implementation Plan for Traceability

Changes to the Australian Immunisation Register (AIR): Legislation amendments

The Government is committed to supporting industry and Healthcare Providers to ensure the safe, efficient, effective and transparent delivery of a pandemic-context vaccination program over an acceptable time period. There is a demonstrated need for legislative changes to improve reporting to the AIR, to better inform vaccine projections, purchasing delivery and program performance, and analyses of vaccine effectiveness and safety.

The changes that are being put in place will ensure Healthcare Providers have improved capability to report vaccinations to the AIR, not just for COVID-19 vaccines but for all vaccines in the NIP. This has the opportunity to improve all vaccine delivery in the future which will be more important than ever for Healthcare Providers and consumers in this pandemic-context.

From 1 **March 2021** it will be mandatory to:

- Report influenza vaccinations and COVID-19 vaccinations to the AIR.
- Record the Batch number field to the AIR. This change is intended to obtain more detailed information on vaccines administered to members of the community. In particular, to improve visibility and responsiveness in the event of any adverse reactions to a particular vaccine brand.

From 1 **July 2021** it will be mandatory to:

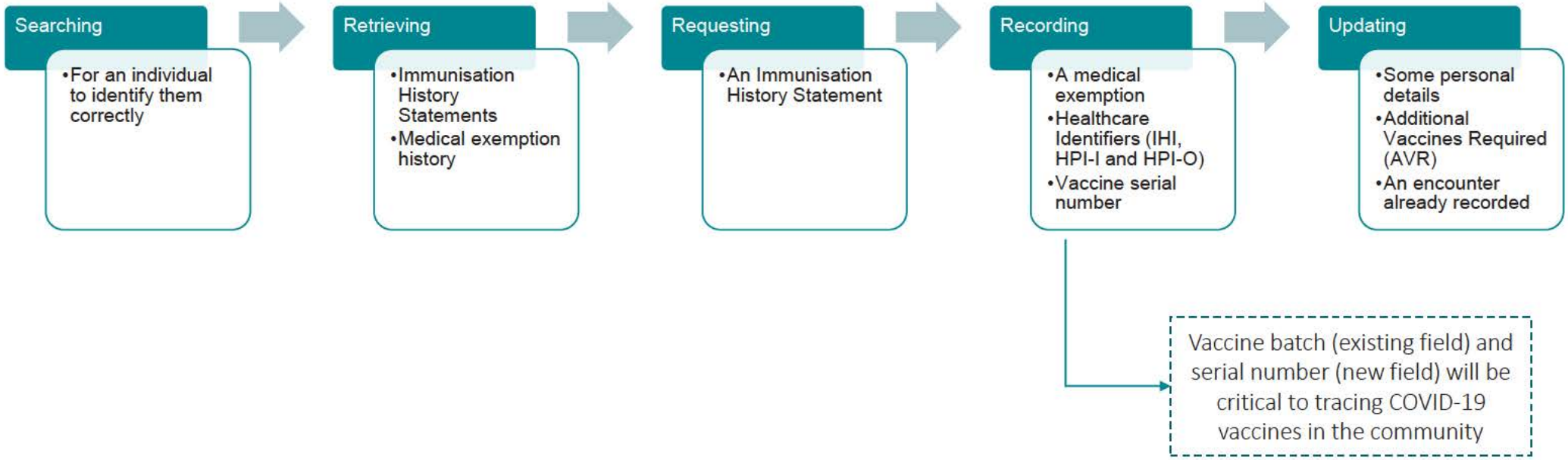
- Report all National Immunisation Program (NIP) vaccinations to the AIR.

Australian Government
Department of Health

Changes to the Australian Immunisation Register (AIR)

There are **new AIR web services** available. These enhancements have been made to support the rollout of COVID-19 vaccines in Australia and improve user experience. As identified in the Australian COVID-19 Vaccination Policy, the AIR will be the unifying national system to monitor both overall immunisation levels and individual immunisation status.

New functionality supports:



Australian Government
Department of Health

Options for development

There are a range of options for development available for all software developers (commercial vendors and jurisdictions):

Develop all available **AIR web services now**:

- ❑ Will ensure you have full AIR functionality and can meet reporting obligations for COVID-19 vaccines
- ❑ Testing and certification will be prioritised

Develop all available **AIR web services in 2 phases**:

- ❑ Do 9 priority web services now and 6 later
- ❑ 2 rounds of developing, testing and certification

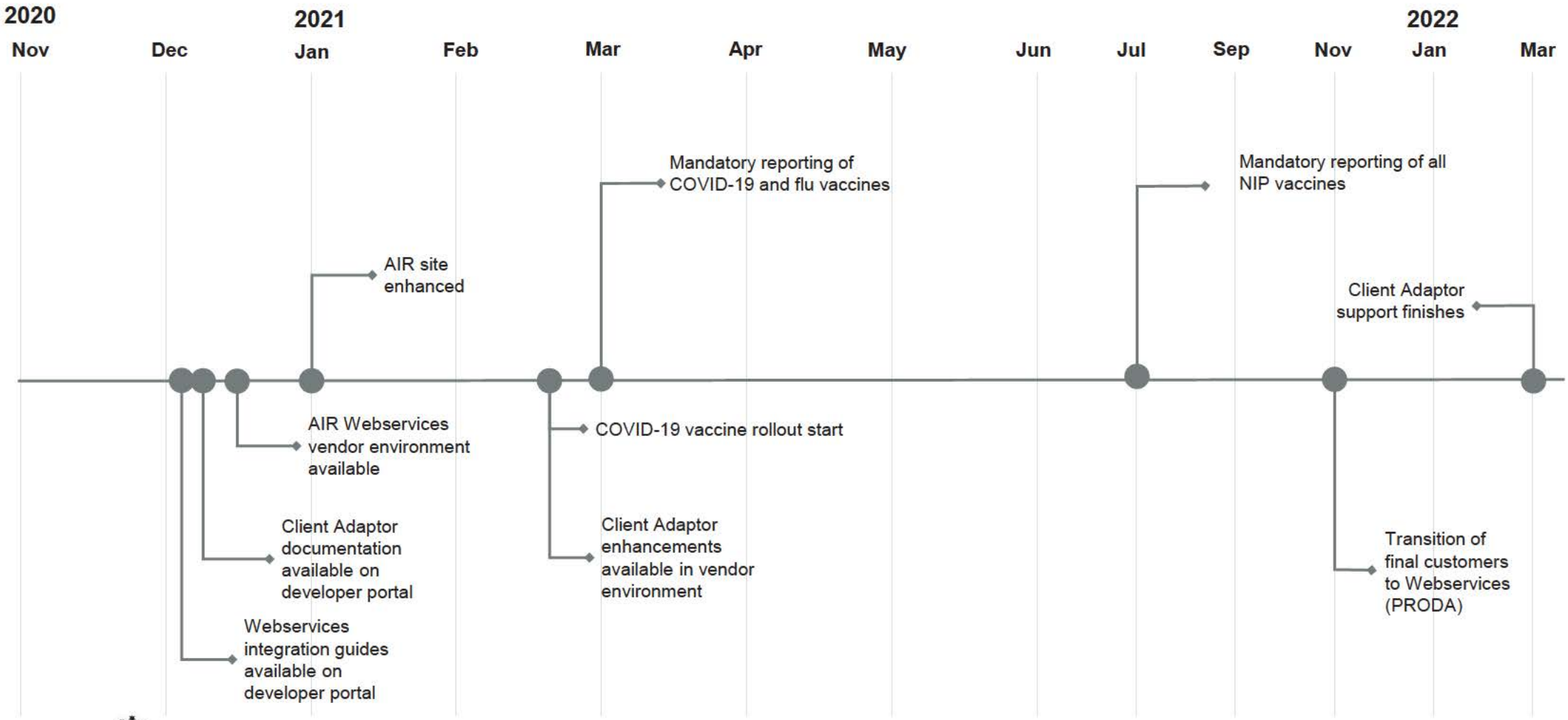
Develop new AIR functionality via **adaptor technology** while transitioning to web services:

- ❑ Code will be available in February 2021
- ❑ Support for adaptor technology will cease in March 2022
- ❑ Only for existing products already connected to the AIR

Resources:

- The Services Australia Software Developer Portal has all the technical specifications and advice about developing AIR functionality
- Developers can email DevSupport@servicesaustralia.gov.au for specific advice and support

Timeline



COVID-19 Vaccination Records and Certification

Digital channels available to access vaccination records include Medicare Online, Medicare express plus app and My Health Record. Patients who cannot use these digital channels can request their Immunisation History Statement through the Australian Immunisation Register Helpline, operated by Services Australia.

All those who are administered a COVID-19 vaccine through the COVID-19 vaccination program will be able to access proof of this vaccination through:

- My Health Record (if they have one).
- Immunisation History Statement (accessed through the Medicare app or online).
- Hard copy record at the time of vaccination.

Australia is also working with the World Health Organization (WHO) as well as other international forums and countries globally on COVID-19 certification. Further information can be provided once available.