Region-Specific Appendix:

Australia and New Zealand (ANZ)

ASCOT ADAPT: Australasian COVID-19 ADAptive Platform Trial

ANZ Region-Specific Appendix Version 2.0 dated 05 August 2021

Summary

This region-specific appendix describes and explains issues related to the ASCOT ADAPT trial that are specific to sites within Australia and New Zealand. This includes issues relating to funding, ethics and governance, drug/domain availability within the region, and proposed sites to be included in the trial.

ASCOT ADAPT: ANZ Region Summary	
Interventions	Refer to study synopsis in core protocol and domain specific appendices. There are no region-specific details to be listed here.
Unit-of-analysis and Strata	
Evaluable treatment-by-treatment Interactions	
Nesting	
Timing of Reveal	
Inclusions	
Domain-Specific Exclusions	
Intervention-Specific Exclusions	
Outcome measures	Primary ASCOT ADAPT endpoint: intensive care support free survival at 28 days. Secondary ASCOT ADAPT endpoints refer to Core Protocol Section 2.3.2 and domain-specific appendices. 1. No additional Region-specific outcome measures

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1. ABBREVIATIONS

ANZ	Australia and New Zealand
CTA	Clinical Trial Approval
CTN	Clinical Trial Notification
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMB	Data Safety and Monitoring Board
GCP	Good Clinical Practice
HDEC	Health and Disability Ethics Committee
HRC	Health Research Council
HREC	Human Research Ethics Committee
ICH	International Council for Harmonisation
ICU	Intensive Care Unit
ITSC	International Trial Steering Committee
NEAC	National Ethics Advisory Committee
NHMRC	National Health and Medical Research Council
RAR	Response Adaptive Randomisation
RCT	Randomised Controlled Trial
RSA	Region-Specific Appendix
RSWG	Region-Specific Working Group
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TGA	Therapeutic Goods Administration
TMG	Trial Management Group

2. PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design. While all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both and commencement of the trial in new geographical regions.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study), a Statistical Analysis Appendix (details of the current statistical analysis plan and models) and Simulations document (details of the current simulations of ASCOT ADAPT), multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain), and multiple Region-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the intervention(s), within each domain, because one of the trial adaptations is that domains and interventions will change over time. Information about interventions, within each domain, is covered in a DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be the subject to a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analysis model will change over time in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis Appendix and Simulations document. These documents are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the Statistics Working Group and the Data and Safety Monitoring Board (DSMB).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase over time. Information that is specific to each region that conducts the trial is contained within a RSA. This

includes information related to local management, governance, and ethical and regulatory aspects. It is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

The current version of the Core Protocol, DSAs, RSAs, and the Statistical Analysis Appendix is listed on the study website (https://www.ascot-trial.edu.au/).

3. ANZ REGION-SPECIFIC APPENDIX VERSION

The version of the ANZ Region-Specific Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1: Approved by the ANZ Region-Specific Working Group (RSWG) on 30th April 2021

Version 2: Approved by the ANZ Region-Specific Working Group (RSWG) on 05th August 2021

4. RSWG GOVERNANCE

4.1. RSWG members

Chair(s): Justin Denholm, Susan Morpeth

Members: James Molton

Andrew Burke

Alison Ratcliff

Michael Maze

Peter Wark

Emily Rowe

Sandy Hodge

Nigel Raymond

Jocelyn Mora

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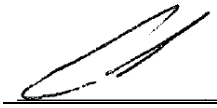
5. ANZ REGION-SPECIFIC WORKING GROUP AUTHORISATION

The ANZ Region-Specific Working Group (RSWG) have read the appendix and authorise it as the official ANZ Region-Specific Appendix for the study entitled ASCOT ADAPT. Signed on behalf of the committee,

Chair Dr Susan Morpeth		Date	05th of August 2021
Chair A/Prof Justin Denholm		Date	05th of August 2021

6. BACKGROUND AND RATIONALE

6.1. Region definition

The ANZ region encompasses all states and territories within Australia, and New Zealand.

6.2. Region-specific background

The ASCOT ADAPT study originated in Australia and New Zealand, and initial ethics, regulatory and funding arrangements have been established in this context. ASCOT ADAPT is expanding to include sites outside this region.

6.2.1. ANZ-specific ethics and regulatory issues

In Australia, human research is conducted under an ethics oversight framework under the auspices of the National Health and Medical Research Council (NHMRC). This includes adherence to Australia's National Statement on Ethical Conduct in Human Research 2007 (updated 2018), and with relevant associated legislation such as The Therapeutic Goods Act 1989 and The Privacy Act 1988. In NZ human research is conducted under an ethics oversight framework as determined by the National Ethics Advisory Committee (NEAC) on Health and Disability Support Services (Kāhui Matatika o te Motu), which was established under section 16 of the New Zealand Public Health and Disability Act 2000. The NEAC issues guidelines that set out the ethical standards that must be met by researchers when they undertake health and disability research and with relevant associated legislation such as the Treaty of Waitangi Act 1975, NZ Bill of Rights Act 1990, Accident Compensation Act 2001, Medicines Act 1981 and the Health and Disability Commissioner Act 1994.

Some relevant differences in consent processes exist between jurisdictions in Australia and New Zealand. For example, surrogate consent processes are acceptable in some Australian jurisdictions, and under certain circumstances, with varying approaches to obtaining and documenting consent to participate permitted. In New Zealand the patient's surrogate can agree that the patient would wish (or not) to consent to participate, and there must be evidence that the treating clinician believes it is in the patient's best interests to participate. ASCOT ADAPT has therefore developed a surrogate consent process which forms part of the core trial protocol, however, this option for enrolment is only activated in jurisdictions which permit surrogate consent to occur, and where approval to do so has been obtained. In all cases, local jurisdictional requirements will be adhered to in addition to any core protocol for ASCOT ADAPT.

6.2.2. ANZ-specific funding issues

Funding provided to support ASCOT ADAPT may be conditional on dispersal within particular geographic boundaries, including limitations on expenditure outside specific countries or sub-jurisdictions. The ANZ RSWG will provide advice to the ITSC regarding receipt and distribution of jurisdictional-specific funding as required.

7. OBJECTIVES

The ANZ RSWG will provide oversight of the trial in the context of Australia and New Zealand. Specific roles of the ANZ RSWG include:

- Advise on case report forms (CRFs) as required
- Engage with the ASCOT Therapeutic Advisory Committee and domain specific working groups regarding availability, feasibility and suitability of potential therapeutic agents within ANZ
- Facilitate engagement with peer groups about the project, including the ASCOT domain specific working groups and pregnancy working group
- Consider ANZ specific issues for any proposed sub-studies
- Advise the ITSC/TMG regarding allocation of funds within ANZ as well as opportunities for further funding
- Advise the TMG regarding ethics and governance issues specific to ANZ
- Identify potential new sites within ANZ and put these forward to the ITSC/TMG

8. TRIAL DESIGN

This RSA will inform all domains conducted as part of ASCOT (see Core Protocol Section 1.4.2). Treatment allocation will be adaptive, as described in the Core Protocol Section 2.4.4.

8.1. Population

ASCOT ADAPT enrolls patients with COVID-19 admitted to hospital who are not requiring intensive organ support (see Core Protocol Section 2.2).

8.2. Eligibility criteria

Patients are eligible for ASCOT ADAPT if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria (see Core Protocol Section 2.2). There are no additional inclusion or exclusion criteria that apply specifically to patients within Australia or New Zealand.

9. TRIAL CONDUCT

9.1. Region-specific data collection

9.1.1. Microbiology

Nil relevant

9.1.2. Clinical data collection

Data for classification of ethnicity will be collected for both Australia and New Zealand. National recommendations for each country will be followed to ensure that appropriate data is collected to allow regionally relevant classification to occur.

9.2. Region-specific regulatory aspects

In Australia, the Therapeutic Goods Administration (TGA) provides regulation of medicines and medical devices, including those used in clinical trials such as ASCOT ADAPT. The TGA provides a framework for clinical trials of medications not licensed within Australia, including registration and safety reporting requirements. Where an unapproved therapeutic good is to be included in ASCOT ADAPT, or an approved therapeutic good is to be used for a different indication, the TGA will be

notified via a Clinical Trial Notification (CTN) or Clinical Trial Approval (CTA). All suspected unexpected serious adverse reactions (SUSARs) and significant safety events (SSIs) that occur within the ASCOT ADAPT trial will be reported to the TGA in accordance with the TGA's requirements for clinical trial reporting and the NHMRC's safety monitoring and reporting guidelines. Australian clinical trials must comply with the Australian Code for the Responsible Conduct of Research.

Medsafe is the New Zealand Medicines and Medical Devices Safety Authority. It is a business unit of the Ministry of Health and is the authority responsible for the regulation of therapeutic products in New Zealand. Medsafe administers the application and approval process for clinical trials under an authority delegated from the Director-General of Health. Medsafe receives and processes applications, liaises with the relevant Health Research Council (HRC) committee and the applicant, and issues approval letters. The HRC maintains standing committees to consider clinical trial applications and make recommendations to the Director-General. The Standing Committee on Therapeutic Trials (SCOTT) considers applications for pharmaceutical-type medicines and must approve use of medicines within trials in New Zealand if that medicine is not already approved by Medsafe for that indication in New Zealand. Section 30 of the Medicines Act authorises the Director-General of Health to approve a clinical trial on the recommendation of the HRC.

In both Australia and New Zealand, ASCOT must comply with the Good Clinical Practice framework. ASCOT is registered with the Australia and New Zealand Clinical Trials Registry as well as clinicaltrials.gov.

9.3. Region-specific availability of and access to trial interventions

9.3.1 Antibody Domain

As of April 2021 there is no antibody intervention available under the trial to sites in Australia or New Zealand. This is due to a lack of local availability and supply of any antibody products that may be beneficial. Antibody therapies may become available in this region in future, at which point these therapies will be detailed in the Antibody Domain-Specific Appendix.

9.3.2 Antiviral Domain

Nafamostat is not registered for use by either the TGA in Australia or by Medsafe in New Zealand. Use in ASCOT ADAPT will be governed by clinical trial registration requirements in both countries (Clinical

Trial Notification to the TGA in Australia and SCOTT approval in NZ). The drug will be manufactured in a facility that adheres to good manufacturing practice (GMP).

9.3.3 Anticoagulant Domain

Thromboprophylaxis for the Anticoagulant Domain will consist of low molecular weight heparin (LMWH), with choice of agent (enoxaparin, dalteparin or tinzaparin) determined according to availability and local practice at the participating site, and dose determined by arm of allocation. All LMWH agents used in Australia and New Zealand as part of ASCOT ADAPT will be medications registered by the TGA and/or Medsafe for use in thromboprophylaxis. Drugs will be procured locally as part of usual management practices.

9.4. Region-specific trial management

The ANZ RSWG will provide oversight of the trial in the context of Australia and New Zealand, and report to the ASCOT ADAPT ITSC. Details of region-specific trial management can be found in the ASCOT ADAPT core protocol.

Sites in the Australia and New Zealand region will undergo externally conducted, periodic remote monitoring during the trial period. External monitoring will be conducted for the first participant enrolled at each site, and for a randomly selected 10% of subsequent participants, and consider issues of trial conduct and data completeness.

9.5. Blinding

9.5.1. Blinding

This will be an open-label trial.

9.5.2. Unblinding

Not relevant.

10. ETHICAL CONSIDERATIONS

The trial protocol and associated appendices, as well as other trial documentation, will be submitted to Melbourne Health Human Research Ethics Committee (HREC) in Australia (and other local

institutional ethics committees as required), and to the Health and Disability Ethics Committee (HDEC) in New Zealand. Sites will not be able to recruit participants until approval has been obtained.

Informed consent will be obtained in accordance with section 2.4.3 of the core protocol as well as the applicable informed consent standard operating procedure (SOP) for each country.

Demographic data regarding ethnicity is being collected within ASCOT ADAPT. This is considered important given the recognised disproportionate impact of the COVID pandemic on racial and ethnic minority groups in many global contexts (1). No pre-planned subgroup analyses based on race or ethnicity are intended, and data will be presented in aggregated form within demographic category reporting.

ASCOT ADAPT seeks to be responsive to and engaged with community priorities in relation to COVID and its impact. Trial primary and secondary outcomes have been developed through broad consultation including focus groups with affected community members. ASCOT ADAPT has an overarching International Trial Steering Committee, including community representation into trial management and monitoring (2).

11.GOVERNANCE ISSUES

The University of Melbourne is the primary sponsor of the trial, and maintains responsibility for all Sponsor activities related to the trial within Australia. Middlemore Clinical Trials have accepted the role as Sponsor within New Zealand and maintain all Sponsor responsibilities within that country. Each sponsor is responsible for obtaining ethical approval for the trial within their country, ensuring adequate trial insurance is obtained, entering into clinical trial research agreements with sites, and complying with all Sponsor responsibilities as outlined in the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

The University of Melbourne has also engaged operational and trial management support from coordinating hubs in Queensland (University of Queensland) and New South Wales (Hunter Medical Research Institute).

Site-specific governance approval (Australia)/localities approval (NZ) will be obtained at sites before they are activated for recruitment.

12.REFERENCES

1. Tai DB, Shah A, Doubeni CA, Sia IG, Wieland ML. The disproportionate impact of COVID-19 on racial and ethnic minorities in the United States. Clinical Infectious Diseases. 2020 Jun 20.
2. Marshall JC, Murthy S, Diaz J, Adhikari N, Angus DC, Arabi YM, Baillie K, Bauer M, Berry S, Blackwood B, Bonten M. A minimal common outcome measure set for COVID-19 clinical research. The Lancet Infectious Diseases. 2020 Jun 12.