Appendix:

BIOLOGICAL SPECIMENS

ASCOT ADAPT: Australasian COVID-19 ADAPTive Platform Trial

Biological Specimens Appendix Version 2.0 dated 2 October 2020

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1. ABBREVIATIONS

ACD	Acid Citrate Dextrose
DNA	Deoxyribonucleic Acid
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMB	Data Safety and Monitoring Board
EDTA	Ethylenediaminetetraacetic Acid
GWAS	Genome Wide Association Study
ITSC	International Trial Steering Committee
PBMC	Peripheral Blood Mononuclear Cells
RSA	Region-Specific Appendix
SST	Serum Separating Tube

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 (see glossary, Section 1.2 Core Protocol for definitions of these terms) 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 Appendix (details of the current simulations of ASCOT ADAPT), multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain), and multiple Regions-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 subject of 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 overtime in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis and Simulations Appendices. These Appendices 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 Safety and 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 in the Protocol Summary and on the study website (https://www.ascot-trial.edu.au/).

3. BIOLOGICAL SPECIMENS APPENDIX VERSION

The version of the Biological Specimens Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1: Approved by the Biological Specimens Working Group (DSWG) on 13th August 2020

Version 2: Approved by the Biological Specimens Working Group (DSWG) on 2nd October 2020

4. BIOLOGICAL SPECIMENS DOMAIN GOVERNANCE

4.1. Domain members

Chair: Associate Professor Justin Denholm

Members: Craig Gedye

Judy Chang

Michael Maze

Priyanka Pillai

Ed Raby

David Paterson

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4.2. Contact Details

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5. BIOLOGICAL SPECIMENS WORKING GROUP AUTHORIZATION

The Biological Specimens Working Group (DSWG) have read the appendix and authorize it as the official Biological Specimens Appendix for the study entitled ASCOT ADAPT. Signed on behalf of the committee,

Chair Date 2nd of October 2020

A/Prof Justin Denholm

6. INTRODUCTION

ASCOT ADAPT contains 4 tiers for collection of data and samples. The *Core* data only includes recording of clinical, outcome, treatment data and results from laboratory testing and does not involve storage of samples.

The *Enhanced biological, Research biological* and domain-specific biological tiers include the collection and storage of some biological samples. The collection, processing, storage and shipping of biological samples will follow local standard operating procedures and regulations for handling and transporting clinical specimens containing infectious materials.

These samples and data collection will be dependent on site capacity and participant consent obtained for enhanced sample collection, storage and sharing.

7. ENHANCED BIOLOGICAL (TIER 1)

Includes research blood, stool and respiratory sampling.

Blood and stool samples for the analysis of potential biomarker assays, immunological responses including but not limited to antibody levels, response to virus and genetic analysis including genome wide association study (GWAS).

Genomics is increasingly informing researcher's understanding of disease pathobiology. Large-scale human GWAS studies require large collections of DNA from people exposed to, or infected with, SARS-CoV-2. To identify human genes related to susceptibility or disease outcome, this would require COVID-19 individuals with well-defined clinical phenotypes, as GWAS are case-control studies that compare phenotypes, i.e. mild disease vs severe disease, asymptomatic vs active disease, survivors vs non-survivors. To ensure large sample sizes of individuals with differing clinical phenotypes it is essential to collect DNA from multiple studies, with diverse study designs. For example, DNA from active COVID-19 cases from the ASCOT study and from asymptomatic exposed individuals from household or population studies.

8. ENHANCED BIOLOGICAL (TIER 2)

Includes additional blood sampling for PBMC isolation and biobanking. Sites that agree to participate in tier 2 sampling, should also have tier 1 samples collected.

9. SCHEDULE OF EVENTS

Table 1. Schedule of Events

Visit Day (+/- 1 day)	Day 1	Day 3	Day 7	Day 14
Enhanced Biological (Optional Tier 1)				
Research bloods[1] (1x9mL SST tube) for biobanking storage	X	X	X	X[2]
Research bloods[1] (1x5mL EDTA tube) for cell pellet (genomic) assay	X			
Stool sample[1]	X			
Respiratory tract[1] sample stored	X	X	X	
Research Biological (Optional Tier 2)				
Research bloods[1] (3x9mL Sodium Heparin and 2x9mL ACD tubes) for PBMC, plasma biobanking storage	X	X	X	X[2]

1. While still in hospital only.
2. If discharged prior to Day 14, collect sample on day of discharge
3. Appropriate commercially available collection tubes may be substituted for logistic reasons after discussion with principle investigators, providing sample volumes are not exceeded.

10. DOMAIN-SPECIFIC BIOLOGICAL

In addition to sample collection detailed in the Enhanced biological and Research biological tiers, specific interventional arms may request or require additional specimens to be collected, such as blood samples for drug levels. Such requirements will be detailed in the relevant appendices. Where samples are collected according to domain-specific protocols, processing and storage will occur according to the general ASCOT ADAPT biobanking protocols and relevant laboratory manuals.

11. STORAGE AND RETRIEVAL

Details regarding collection of samples, handling and processing for storage will be provided to sites through relevant technical laboratory manuals. All specimens collected for ASCOT ADAPT will be stored in participating laboratories according to laboratory manuals, and registered in a secure, purpose built electronic database, allowing subsequent retrieval of specimens as required. Samples collected will be stored indefinitely for later research access.

It is anticipated that external researchers will request access to biological samples for a variety of research projects. Applications will be considered Samples will only be released to researchers whose research has been approved by an appropriately constituted Human Research Ethics Committee. The Human Research Ethics Committees will review the research to ensure that it is ethically and scientifically sound and will be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

Publications arising from studies undertaken using ASCOT biobank samples will have authorship determined in the following way: Primary and senior authorship will be determined by the Biobank steering committee, in accordance with intellectual contribution to the specific project. All hospitals and participating organisations contributing at least one case to the Biobank will be listed as ‘ASCOT biobank investigator group’. Hospitals contributing at least one case to the Biobank will nominate a locally determined coordinating investigator for inclusion, in alphabetical order. For example: “Smith A, Jones B, Malik C and the ASCOT biobank investigator group” with full author details listed following the manuscript.