WESTERN AUSTRALIAN

COVID RESEARCH RESPONSE

A Proposal to fund Phase 1 of a world-leading data analytics initiative tackling our biggest health threat this century

Executive Summary & Recommendations

The global impact of COVID-19 is profound with severe implications for citizen health, the economy and possible public order threat.

Western Australia is the last advanced medical jurisdiction in the world to have sufficient time – albeit only a matter of weeks – to plan a clinical response to treat COVId-19. Currently there is no proven treatment or cure. Globally, hospital research to prevent has floundered due to overwhealming clinical caseload and redirection of staff. However, Western Australia has the opportunity to act now. We are ideally placed to be the epicentre of research and development into COVID-19.

We have developed a automated platform of patient data collection through hospital IT systems coupled with patient sample collection, enabling research to continue in the pandemic. Further, UWA & Murdoch are collocated with the largest hospital in the state, and ideally suited to facilitate patient clinical data and also patient samples. The Australian National Phenome Centre is the largest most advanced experimental laboratory in the southern hemisphere, able to process samples in a real time fashion, accurate to produce a chemical fingerprint of a patient's health today. The ANPC sits in the same university building at FSH and there is direct access to thePusey supercomputer.

Consequently researchers from WA can access real time patient clinical data combined with outstanding laboratory analyses, that can be processed through the WA supercomputer network. Different approaches to understanding the infection that are relevant to both individual patients and the general population will be examined to triangulate treatment and outcome effects.

The outcome will be a genuinely world-leading, WA response to the viral threat. The set up and foundation of the CRR will be and be a critical base for research and clinical trials conducted in WA, now and for decades to come.

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Introduction

The global impact of COVID-19 is profound with the health and possible public order threat complicated by the highly linked economic fragility and volatility that this uncertainty brings.

The public health threat it represents is the most serious seen in a respiratory virus since the 1918 H1N1 influenza pandemic which killed 50 million of the 500 million people infected worldwide, according to the Medical Research Council Centre for Global Infectious Disease Analysis at Imperial College London.

COVID-19 virus poses a singular threat to society if immediate action is not taken. The virus is new and there is much to learn about infectivity and individual and population risk in a very short time. Since its emergence there has been considerable progress made in developing tests for COVID-19 with a reasonably rapid turn-around time of a few hours.

However, a critical unmet need remains in understanding how the virus establishes itself in the host with substantial variation in susceptibility in impact; from little or no apparent effect to death. Understanding the pathways to infection and the biological consequents will enable the development of effective treatments and vaccines to mitigate the current threat as well as to prepare for subsequent viral incursions which at sometime soon will almost certainly be more catastrophic.

An Immediate problem is that there are no specific therapeutic agents approved as effective for coronavirus infections. All the promising treatments thus are "off-label". Some of these treatment options include antiviral (Remdesivir); antimalarial (chloroquine/ hydroxychloroquine); combination of two HIV drugs Lopinavir/ ritonavir and the same two HIV drugs along with anti-inflammatory interferon beta. Other potential drug treatments include antibiotics/antiparasitics, nonspecific anti-inflammatory and immunosuppressive drugs and monoclonal antibodies. There is a need to appropriately test these and other emerging therapies.
A recent review of these identified therapeutic prospects has questioned the reliability of the results gained and pointed to volatility in the outcomes, due to small sample sizes and lack of quality data. The only randomised trial to date showed a lack of superiority of any treatment and notably highlighted the significant side effects of the experimental therapies. Consequently, 'best opion' treatments may be causing more harm than good.

The ambiguity of the results from these studies underlines the absolute demand for high quality data needed to procide clinical evidence regarding COVID-19 treatments, with targeted personalised care being the goal to improve personal and system outcomes.

Western Australia is ideally placed to lead an international research program of attack to COVID-19. We propose a harmonised platform of integrated research to clinical care in W.A. The WA COVID Research Response (CRR) team brings together researchers, scientists and clinical trial teams under the WAHTN as 'one voice' in collaboration, building a coordinated response for WA. The immediate core bojective is to build a platform for realtime accurate patient data supported by biological samples that can be relayed in a deidentified manner for all researchers and scientists.

In anticipation of a global pandemic, the World Health Organisation (WHO) supported the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC), to develop a rapid response platform for clinical trials to Severe Acute Respiratory Infection (SARI). The protocol enables and outlines accurate protocols for data and biological samples to be collected in a globally harmonised manner. The benefits include; improved data quality, reduced error of measurement and increased statistical power through the ability to combine, compare treatments and outcomes on a grand scale by statistical means. This standardised protocol was approved by the WHO and designed to be used for coordinated clinical investigation of suspected or confirmed cases of COVID-19.

The WA COVID Research Response (CRR) team is leading this WHO ISARIC platform in a state-wide collaboration. The team comprises senior clinicians, researchers and administrators in the WAHTN network.

- CRR has set up the DoH REDCAP database to record details of all patients presenting with SARI in a standardised clinical pathway. This REDCAP system has been coordinated 'handshakes' established with all metropolitan hospitals as well as the

W.A. Country Health Service. This will enable a streamlined coordinated platfrom. Data will provide clinical uploads for patient care and simultaneous data warehousing.

- CRR has enabled ethics and governance approvals for an integrated combined biobank of laboratory samples as part of routine care incorporating; storage of excess from daily clinical samples and additional specific samples for experimental, laboratory and genetic analysis. This is particularly relevant in WA research projects, as we can work in collaboration with the Australian National Phenome Centre (ANPC), who have made available their considerable resource to help.
- CRR will provide coordinated high-quality data in patient data and biological samples to all W.A. researchers through the WAHTN. This platform provides a template for all research analytics and will coordinate the data interrogation and interpretation at a State, national and international level.

As a team the entities are uniquely placed to facilitate the WA state-wide research strategy with coordination through WAHTN. CRR is building the integrated data and sample platform for all health systems to copy and collaborate to deliver hard science about the COVID-19 infection. The physical colocalization of key units place WA in an ideal position for this project, for instance; the Australian National Phenome Centre is situated in the Harry Perkins (South) building adjacent to the Fiona Stanley Hospital. This is co-located with the CRR, the Biobank and is proximal to PathWest Laboratories and clinical activity.

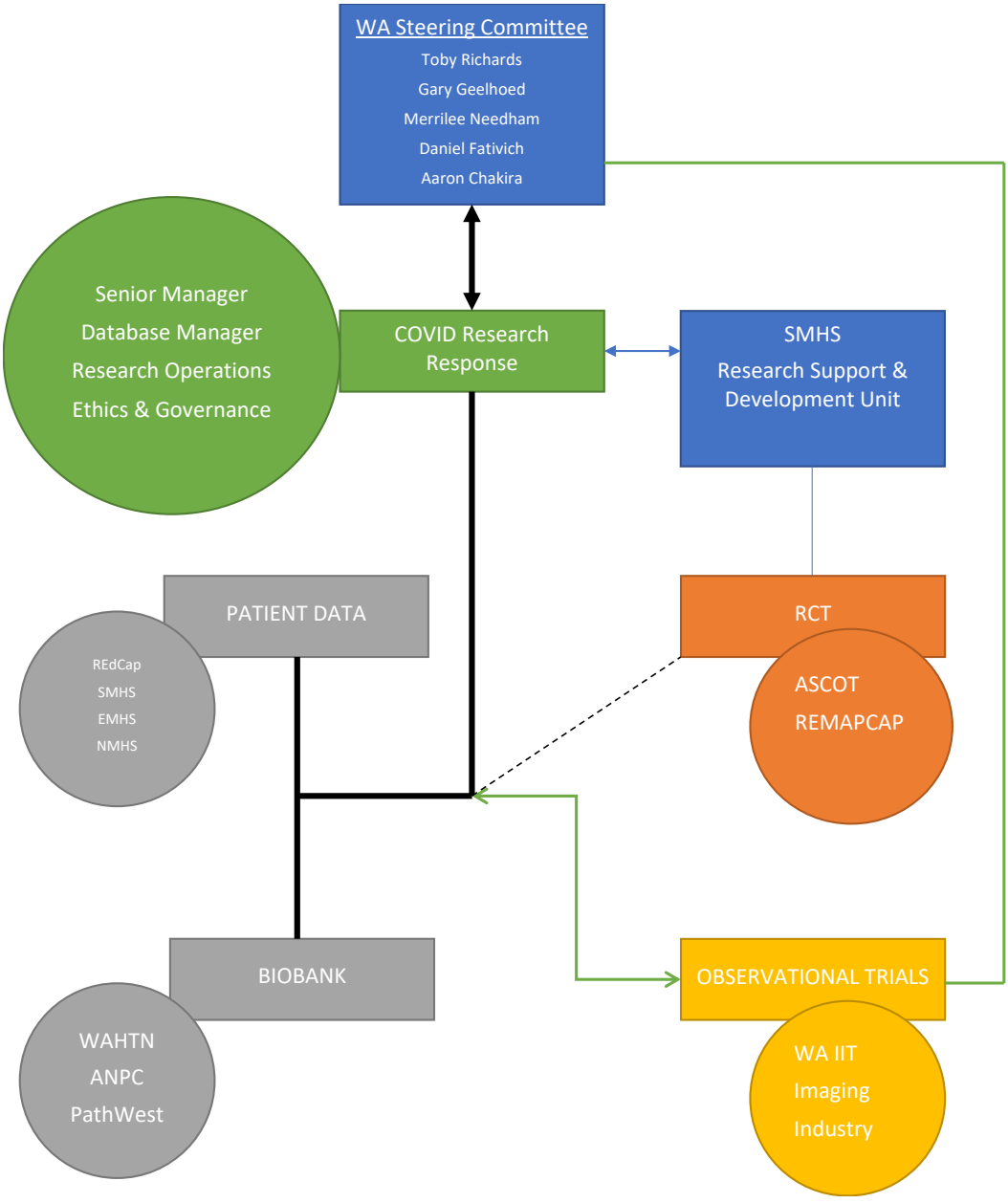
In collaboration with the ANPC and the WAHTN network this will enable all researchers access to high quality data, samples and analysis minimising duplication, reducing costs and maximising output for patient care.

Clinical sample and data collection can commence within the next two weeks. Different approaches to understanding the infection that are relevant to both individual patients and the general population will be examined to triangulate treatment and outcome effects. The outcome will be a genuinely world-leading, WA-driven, response to the viral threat and be a critical part of the clinical trials conducted in WA (please see appendix for supported trials).

CRR Personnel

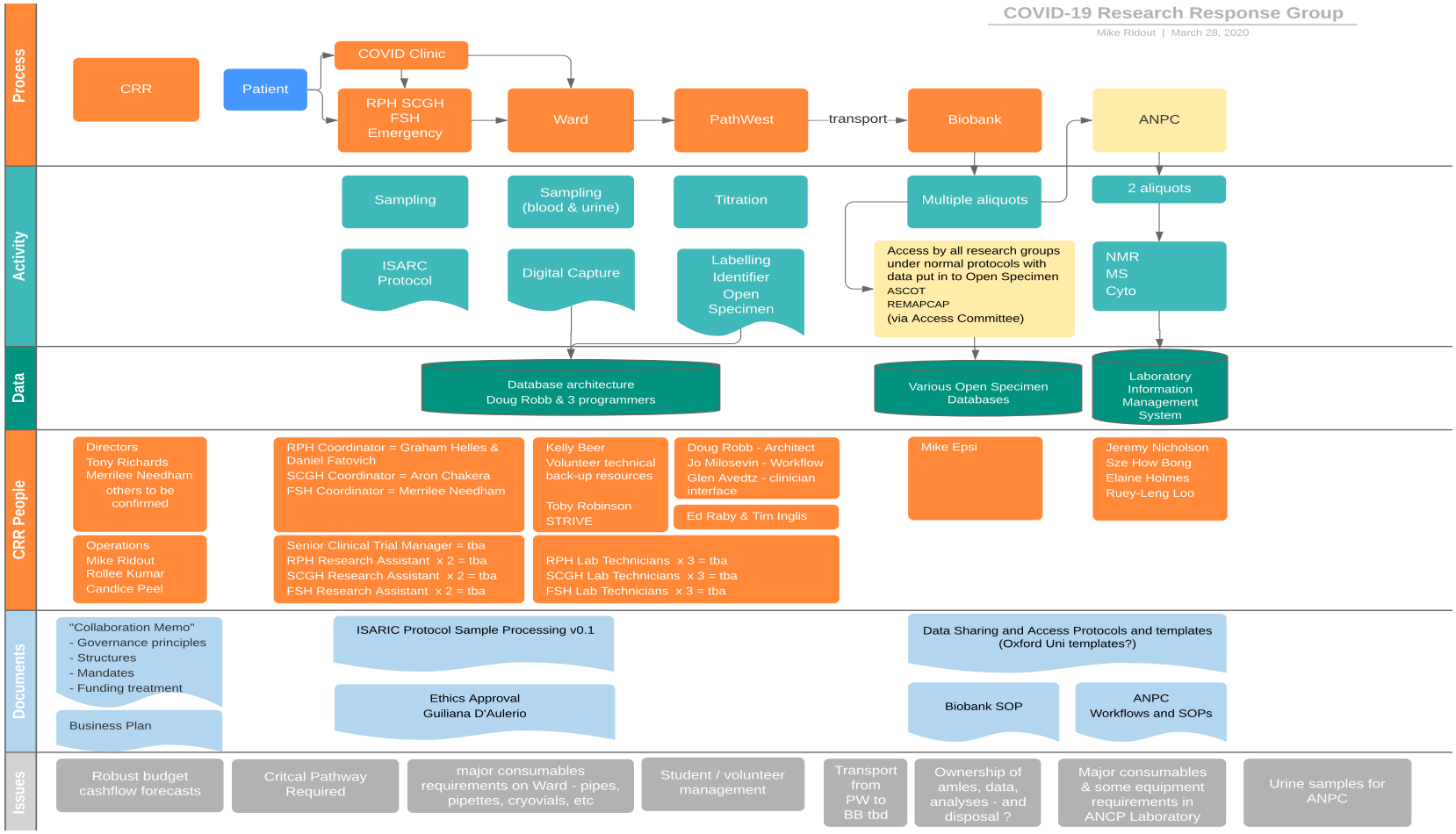
WAHTN leadership	@Gary Geelhoed
CRR directors	@toby.richards@uwa.edu.au & @Needham, Merrilee
Ethics	@Giuliana D'Aulerio (tbc new appointment next week)
Clinical Trials Liason	@Giuliana D'Aulerio
Operations Managers	@mike.ridout@murdoch.edu.au @Rolee Kumar
Database manager	@Doug Robb
Pathwest liason	@Raby, Edward @Tim Inglis
Biobank Manager	@Michael Epis
Sample analyses and coordination	@Sze How Bong
ANPC	@Jeremy Nicholson
SMHS Research Director	@Needham, Merrilee
EMHS Research Director	@Fatovich, Daniel
NMHS Research Director	@Chakera, Aron
SMHS Management	@Edgar, Dale
EMHS Management	
NMHS Management	@Thomas Gilbert
Community Integration	@Christopher Reid
Workforce planning and coordination	@Kelly Beer
Post Graduates	@Jay Jay Jegathesan
Medical Students	@STRIVE WA
Financial Managers	@Candice Peel @Sue Geoghegan

CRR Outine Structure

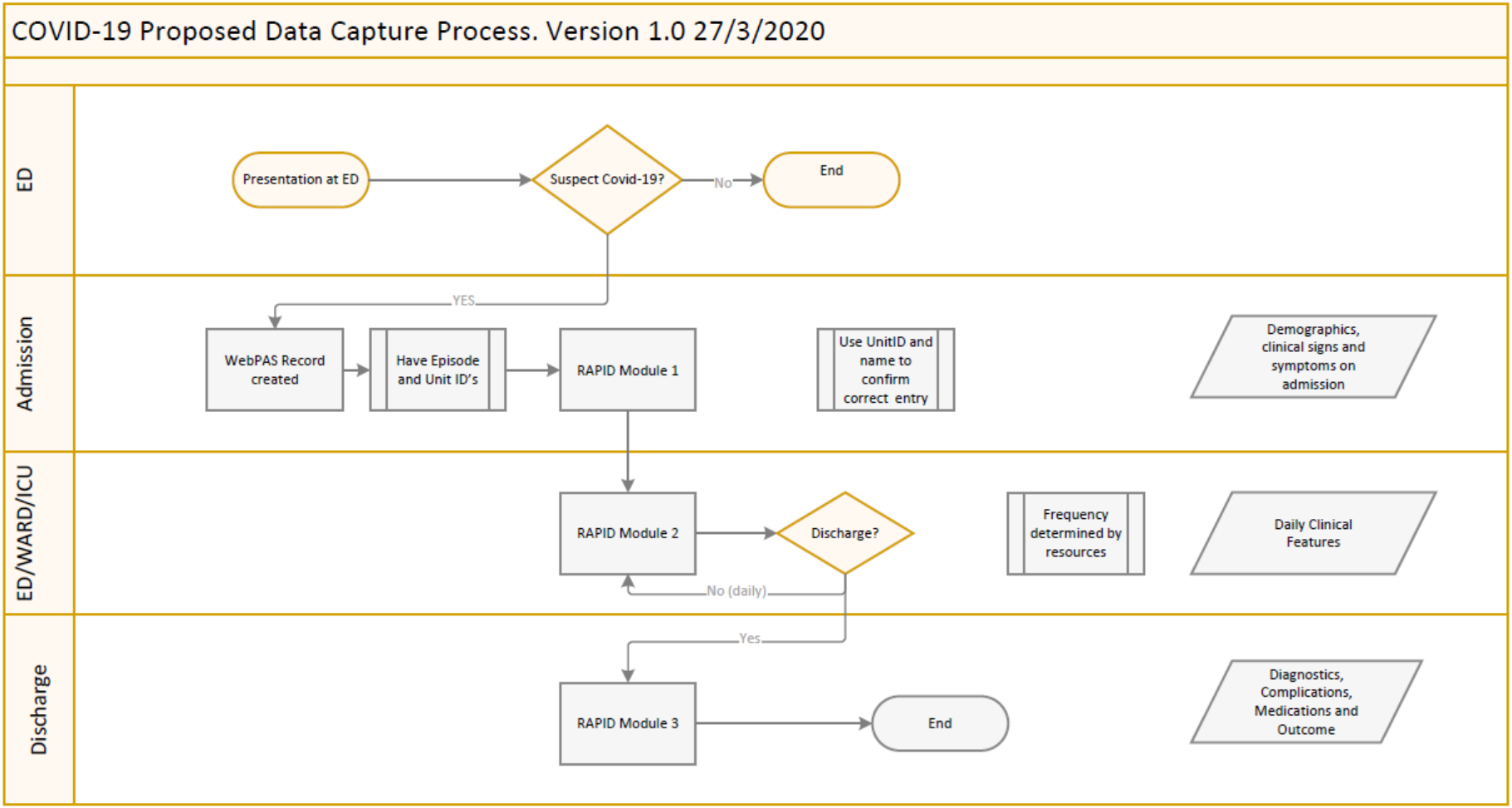


Outline of Covid Research Response: The CRR aims to capture high quality patient data and biological samples that are available to all researchers in WA. WAHTN will ensure that researchers will be made aware they can access this through *open specimen*. All studies can approach the working group for access to samples and data. The CRR will help coordinate ethics, MOU, MTA's etc and facilitate open communication and collaboration between groups to avoid duplication and data sharing.

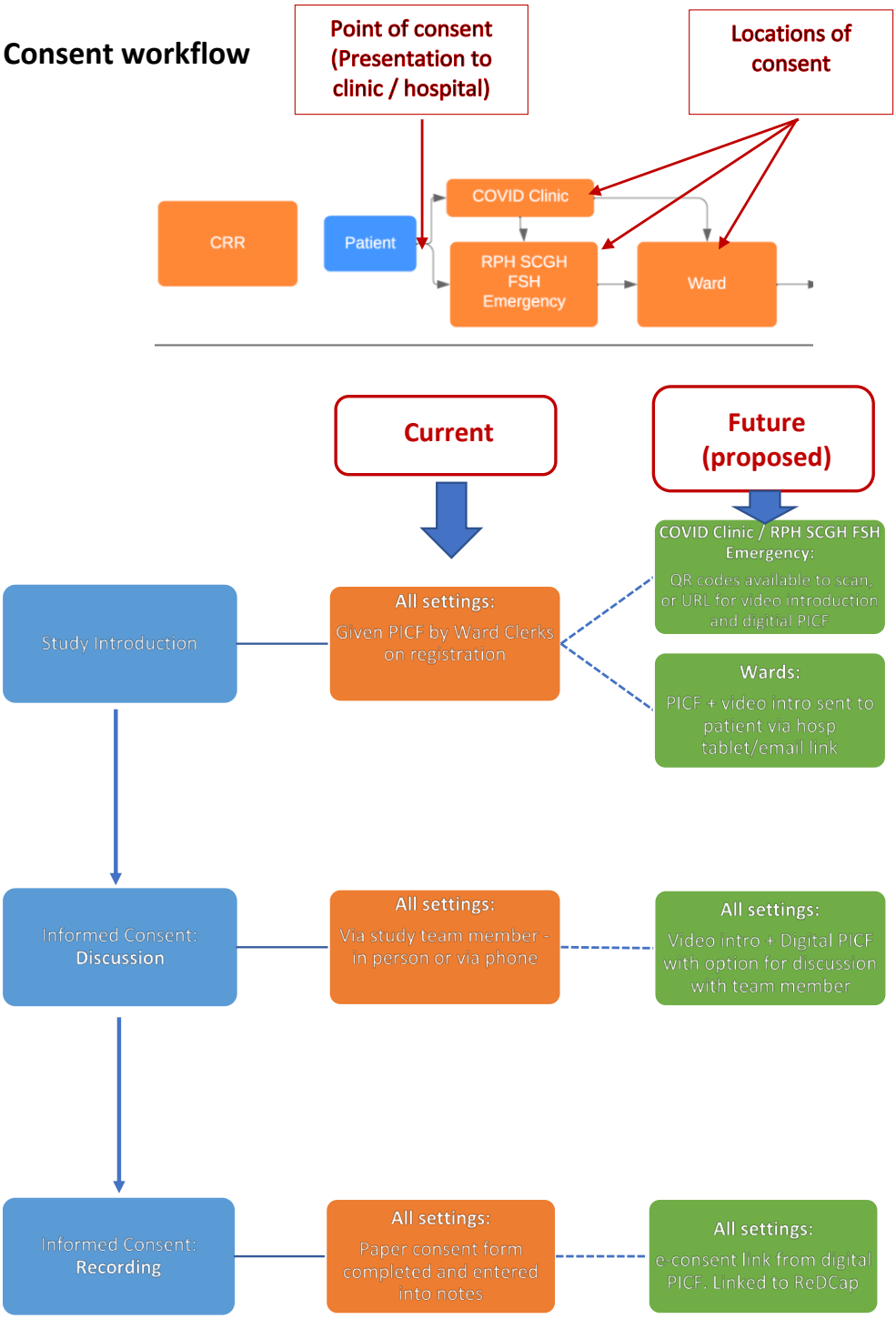
Workflow Schematic



Data Capture (REDCAP)



Consent Workflow



Budget Information

The urgency with which the WHO ISARIC data collection platforms and analytical readiness protocols are developed cannot be over stated. By end of week we must have in place an operational team to manage incoming data and to process it, before national and hospital restrictions on movement and social isolation.

Prior to that we must have operational platforms capable of accepting the patient data and sample prior to creating useful information. Thus we have three concurrent phases:

(A) Administration set up
(B) Patient Data, Clinical Infrastructure & Sample Collection
(C) Rapid Analytics and Translation.

Each is outlined and preliminary costing indicated below.

A Core Infrastructure hub has been established at Perkins South with linkage to all hospitals. This has been run by collaborative individuals diverting their existing funds and manpower in 'good will'. This group is working "hand in glove" with the Murdoch ANPC and Genomics Core facility as well as the WAHTN and each Metropolitan Health System.

A: Administration Setup – Target Timeline Friday 3 April
1 FTE Senior Trial manager coordinating oversight for CRR. (TR currently supplying) ($117k)
1 FTE Project Manager to coordinate funding, HR, contracts MOUs and IP ($150k)
1 FTE Trial Manager coordinating trial protocol harmonisation, ethics & governance ($117k)
1 FTE Database Manager coordinating portals & platforms (Murdoch supplying) ($150k)
1 FTE Biobank Manager ($140k)

B: Clinical Infrastructure and Sample Collection: Target Timeline Thursday April 8th
Laboratory technicians to be placed into PathWest to enable sample collection for both Tier 1a & Tier 1b samples
2 FTE FSH ($240k)
2 FTE SCGH ($240k)
2 FTE RPH ($240k)
1 FTE Senior Database Manager to oversee large data storage, quality, validity and version control. Interface to patient data (REDCAP), diagnostic pathology (PATHWEST) and BIOBANK data in a deidentified manner to all researchers. ($150k).
1 FTE Project Manager to coordinate between the WA hospitals for data collection, also with ANPC and pan-WA researchers to facilitate research, remove duplication, promote collaboration and minimise research costs. ($130k) (currently aided by WAHTN)
3 FTE Trial Managers to facilitate clinical trials conducted via the research template to explore novel therapies to treat COVID-19, one for each metropolitan healthcare region. One currently supported voluntarily @EMHS and @SMHS ($450k)

- Consumables, to cover blood and urine sample collection, also PAXgene storage for genetic analysis ($1453 per 100 samples). It is envisaged that of 2.5 million people in WA, we will collect data on 100,000 patients in the next six months. This will require 1000 packs ($1.75m).
- Open label biobanking system ($45,000)
- 2x -80c freezers @ 35k each for sample storage ($70k)

C: Rapid Analytics and Translation: Target Timeline end April
Laboratory technician staff and Bio-informatician to be placed into ANPC
3 FTE ANPC ($380)
Consumables and minor equipment ($220)

Applying a discount factor allowing for the volunteer workforce and in kind contributions being made to these activities, balanced with an expected attrition rate of the workforce and need for personnel redundancy for inevitable COVID-19 incidence, the liability spend is estimated;

April	$ 300
May	$ 400
June	$ 650
July – Dec	$1050

Volunteer Workforce

Background
Engagement of volunteers to support COVID-19 research across sectors and institutions offers an unprecedented opportunity for WA-wide collaboration, promotion of research, and enhancing research training across the state.

Academic staff responses
Responses as of Sunday 29 March 2020 (Total = 55):

Research Delivery	Data/IT	Lab/Biobanking	Other
23	2	11	19

Volunteers will be kept informed of progress of the programme set-up and will be called on as specific skills required, and/or contacts handed to workstream leads to coordinate their involvement as necessary.

Post doctoral Students
Universities are currently collating details of all students undertaking research projects that are prevented by the COVID pandemic. These can be reallocated to support existing students and potentially moved to developing COVID trials (47 current ideas registed with the CRR).

Medical Students
Medical Student representatives from Curtin, UWA and UNDA will coordinate via STRIVE.
The medical student population is ~1,500 across the 3 institutions.
Research provides opportunities for students to meet AMA learning objectives -see below

Further Information
Discussions are currently open with SMHS to ensure appropriate access permissions and insurances for volunteers working within the project.
Discussions are currently open regarding research training resources and support for volunteers who are new to the clinical research environment.

STRIVE

The Student Research Initiative of Western Australia, STRIVE WA, is a research collaborative led by medical students from the University of Western Australia, the University of Notre Dame Fremantle and Curtin University. Our roles cover three key domains:

i) To facilitate medical student participation in audit and research.
ii) To foster the growth of audit and research skills through active participation in all stages of the project cycle.
iii) To advocate for student involvement in projects where there is opportunity.

In light of the COVID-19 pandemic, STRIVE WA has liaised with the state's three medical schools to oversee research-related activities in response to the outbreak. We are passionate about helping the healthcare system, devoted to playing a role in mitigating a potential health crisis and have the numbers to do so.

Our primary and secondary objectives are to:

1. Meaningfully contribute to the COVID-19 response through research-related activities
2. Enhance student learning experiences during withdrawal from clinical placements

Professor Toby Richards set up and has worked successfully with STRIVE WA in the past and is a strong advocate for student involvement in audit and research based on the platform: - STARSurg – STudent Audit and Research in Surgery

Students are able to adapt and bee medically engaged from a more isolated working environment. The following graduate outcomes which apply to this initiative have been transcribed from the Australian Medical Council's 'Standards for Assessment and Accreditation of Primary Medical Programs' (see appendix for further details).

University support

Circular sent by UWA, 30/03/20.

Research opportunities with COVID Research Response (CRR) team and STRIVE
In light of the COVID-19 pandemic, Western Australia hopes to take effective measures to mitigate the deleterious effects of the impending disaster. A cohesive, pan-WA response from the COVID Research Response (CRR) team and Student Research Initiative of Western Australia (STRIVE WA); alongside UWA, the University of Notre Dame and Curtin University will underpin all research efforts.

In the coming days, an expression of interest (EOI) form will be made available to all medical students in WA. This form will be used to develop a database of students who are willing to contribute to COVID-19 research, in any capacity.

As a guide, students will be requested to dedicate 5-10 hours per week to research-related activities with potential for more if desired. At this stage students will work from home or in the education centre of Harry Perkins South, under social distancing requirements. Students will be allocated to mini-teams of 6-18 people, with a chief investigator to oversee the team's function. Project duration will vary depending on its nature.

Desired skills include Good Clinical Practice (GCP), REDCap and/or informed consent training. These skills are not pre-requisites and we encourage everybody to apply, irrespective of year level and experience. Links to these training programs are below.

Due to the rapidly evolving circumstances, there are not yet any concrete research projects, however there are at least 47 in the pipeline. Through this research you have a unique opportunity to make a difference to the local, national and global response to the pandemic whilst gaining invaluable experience. Please contact strivewa@gmail.com to arrange for further discussions.

GCP - https://www.google.com/url?q=https://globalhealthtrainingcentre.tghn.org/ich-good-clinical-practice/&sa=D&ust=1585474855297000&usg=AFQjCNFubKquR7gPDch2wM-r2AO3--EKuw
REDCap - https://www.google.com/url?q=https://projectredcap.org/resources/videos/&sa=D&ust=1585474807600000&usg=AFQjCNFzd3OspOj_2_QTEJikqPZgE9xDBg
ITHS REDCap - https://www.google.com/url?q=https://www.iths.org/investigators/services/bmi/redcap/curriculum/&sa=D&ust=1585474807600000&usg=AFQjCNG0lbiG-5qIO0HKbGLZSFxAxO3jTQ

Ethics & governance

ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections COVID-19 Research Response Trial; ISARIC CCP Version 3.1 (SMHS Version 1.1 26 March 2020)

- WA Health Ethics Application Form (WA HEAF) -COMPLETED
  - Initial submission of protocol, PICF (adult), WA HEAF (V1 20th Mar 20)
  - TR attended HREC meeting on 24th Mar 20
  - Committee report PICF received on 25th Mar 20 and protocol on 26th Mar 20
  - Updated protocol and PICF (V1.1 26th Mar 20) submitted on 26th Mar 20
  - Email verification documents have been validated 27th Mar 20

WA Health sites selected for trial: FSH, Fremantle, Rockingham, RPH and SCGH. Other sites can be added but will require an amendment to be submitted via RGS. Lead members in RGS are Toby Richards, Merrilee Needham, Ed O'Loughlin and Glenn Arendts. RPH PI is Tom Gilbert (Graham Hillis Trial Manager) & SCG Aron Chakera.

Governance in RGS-COMPLETED
FSH Site Specific Assessment Form (SSA Form) completed addressing project details, NHMRC field areas of research, credentialing and training, participants, recruitment, indemnity, insurance, research agreements, IP, biosafety, resource and budget and funds management. FSH budgets authorised for UWA, Murdoch and Health Information

Governance in RGS-PENDING
FSH SSA form final sign off from Jim Gray (Service 2 Business Manager) and Chris Caltsounis (PathWest). FSH budget authorisation from Anaesthesia (Alex Swann), ED (Vanessa Clayden) and PathWest (Linda Leung). Once SSA signed off and budget authorised, TR to sign off then can be submitted to FSH RGO for review. SSA form and budgets for Fremantle, Rockingham, SCGH. Tom Gilbert completing for RPH pending FSH approval.

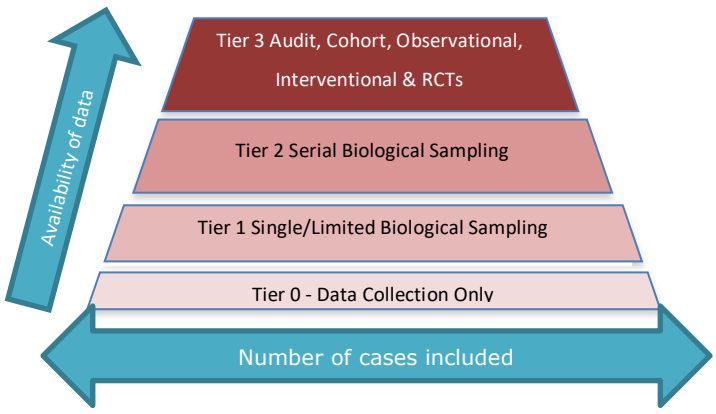
Summary of Protocol

Tier 0 (Clinical data collection) – ISARIC eCRF & RAPID minimum dataset
AIM: Harmonised clinical data capture throughout WA.

Tier 1 (Single biological sample) – BioBank samples
1a Excess / leftover samples from PathWest
AIM: To develop an automated collection of samples to a biobank.
1b Samples for the purpose of research
AIM: To Biobank specific series of plasma/serum and samples.

Tier 2 (Serial biological sampling) – Repeat sampling
AIM: To develop a repeat sampling (from 1b) over hospital admission and discharge.

Tier 3 (Audit, Cohort, Observational and RCTs)
AIM: The coordination of proposals for clinical trials at SMHS. To be templated on top of data from Tiers 0-2. To avoid duplication and repetition. Minimising research staff risk & time and maximising opportunities (please see appendix A for examples of proposed trials)



Pathwest ISARIC protocol sample processing SOP

Two streams of samples will be collected –

ISARIC 1a routine blood tests, the excess eft overs'
ISARIC 1b research

These samples should all be considered to contain Sars-CoV2 and handled under PC2 conditions in accordance with AS/NZS 2243.3:2010 Safety in Laboratories Part 3: Microbiological Safety and Containment.

Labels
Bedside: Addressograph
Laboratory: Generate linear barcodes from ULTRA, affix duplicate label to request form

Storage
Immediately after processing, all aliquots to be frozen at -80 °C for temporary storage
Long term storage at -80 C at Perkins South. Time of freezer storage must be recorded.

Timing
Research samples will be collected only during office hours
Aim to freeze research aliquots within 2 hours of collection, if received out of hours then refrigerate at +4C until processing
Routine samples collected at any time refrigerated at +4C until processing
EDTA processing within 4 hours of collection
PST processing within 2 hours of collection

Routine samples
Plasma separator tube
automated aliquot on track
2-3 x 0.5ml aliquots plasma
EDTA once requested tests complete
Spin
2-3 x 0.5ml aliquots plasma
1 aliquot buffy coat

Dedicated research samples

1 x 10mL DARK GREEN Heparin Plasma tubes with no gel
10 aliquots x 0.5mL of plasma
1 aliquot x buffy coat
1 x 10mL PURPLE EDTA Plasma tube
10 aliquots x 0.5mL of plasma
1 aliquot x buffy coat
1 x RED serum tube (10 mL) with silica clot activator
10 aliquots x 0.5mL of serum
1 x Paxgene RNA tube
Invert Paxgene 10 times then stand at room temp for 2 hours prior to storage at -80C
Urine in 70mL urine container - 8x1ml aliquots

Biobank

Oversight

With Medical Research Future Funds (MRFF), WAHTN commissioned a scoping project in 2018 to develop recommendations for national guidelines and piloting infrastructure for a scalable, shared, and standardised data repository of clinical and research genomics resource facility in WA. The project, overseen by Dr Aron Chakera, has the potential to be scaled to national activity and has produced an international scan of Biobank resources, facility ethics and economics across Australia, the UK and Japan. Currently, a database of all existing capacity has been compiled from WA stakeholders to to support the immediate CRR project.

Future plans will address feedback on the establishment of a centralised biobank in WA

WAHTN has investigated the TKI biobank cataloguing system https://www.openspecimen.org/ This will provide researchers throughout WA access to see what samples are being stored in real time, further the availability of samples and those tests already performed. Consequently, this will avoid duplication of investigations and maximisation of collaborations with significant cohesive data output, with out waste

Current Set up

A Biobank manager was appointed last week and 5 x -80'C frezers unpacked and switched on in Perkins South. Security has connected the freezers to BMS and we are waiting for temperatures to stabilise over weekend before arming the alarms for the freezers (Basement Perkins South).

Discussions between all parties to establish sample types and consumables required for collection sites, labelling and banking protocols. Communications with OpenSpecimen have started to set up the WA online repository with testing commensing this week.

Next Steps

- Purchasing of Freezer racks, Cryoboxes (small and large) & Cryovials.
- Consumables for central site and external sites.
- Computer requirements/availability for baseent freezer area and/or office for biobank Computer system requirements to handle Open Specimen etc.
- Data extraction protocols from OpenSpecimen for samples retrieval and replacement.
- Establish collection protocols for all samples from reciept to storing at offsite locations.
- Protocols for off sites to central Perkins South Facility.
- Protocols for movement of samples between basement and ANPC.
- Determine equipment needs for each site and central depository
- Set up RPH, SCGH and FSH Pathwest centres.
- Staff for sites for sample collection and organisation.
- Establish freezers & freezer service contracts

Australian National Phenome Centre

World-leading researchers at the ANPC are working to revolutionize the diagnosis, prevention and treatment of serious health challenges like cancer, Alzheimer's, autism, obesity and Type 2 diabetes.

By analyzing the molecular, physical and biochemical characteristics of biological tissue and fluids such as blood and urine, researchers at the ANPC aim to predict the complex genetic, environmental and lifestyle interactions causing disease.

The work of the ANPC supports almost every area of bioscience. It reaches across traditional research silos and fosters a new, more collaborative approach to science. Long-term, the ANPC working with State, National and International partners will build 'global atlases' of human disease, providing insights into future health risks, which everyone on the planet can benefit from.

The ANPC uses the largest collection of mass spectrometers in the Southern Hemisphere, combined with nuclear magnetic resonance spectroscopy and advanced data modelling, to identify the unique metabolic 'signature' of individuals and communities.

One of the great strengths of the ANPC is its broad and deep metabolic analysis capacity-designed for clinical diagnostic and prognostic biomarker discovery together with capacity for large scale epidemiological studies.

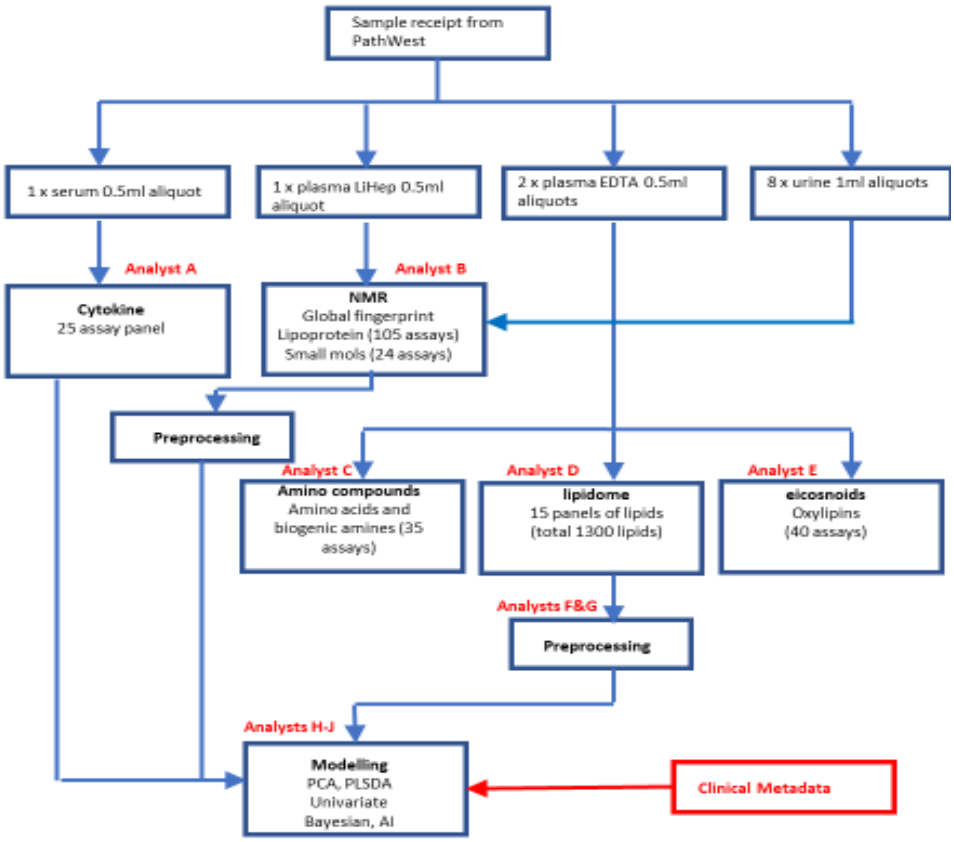
The COVID-19 Challenge

The recent emergent global threat of COVID-19 underpins the need for facilities like the ANPC that can perform high quality biomarker discovery on infectious samples at large scale. This is a problem that spans population health and disease prevention plus acute patient care and optimization of clinical trials- there has never been anything quite like this in modern times.

Nowhere in the clinic is the ability to deliver a rapid prognostic metric of clinical condition more important than in the critical care setting, where a gain in minutes or hours with respect to choosing and implementing a therapeutic strategy can mean the difference between life and death.

We are able to profile and model thousands of metabolites that create the distinctive signatures of disease and to use these for stratifying patients with mild and severe disease and potentially predict outcomes of infections as well as actively monitoring clinical trial interventions to understand the molecular basis for differential responses to therapy.

Workflow



Cover in hand (in budget in process of hiring in purple; requested specialists not yet approved in green

Analyst A (1) x 4	Analyst F (1) x 2 *
Analyst B (1) x 3 +1	Analyst G (1) x 2 *
Analyst C (1) x 2 +1	Analyst H (1) x 2 +2 *
Analyst D (1) x 2 +1	Analyst I (1) x 2 *
Analyst E (1) x 2	Analyst J (1) x 2 *

*Low risk as the bioinformatician posts are self isolating and less likely to be affected

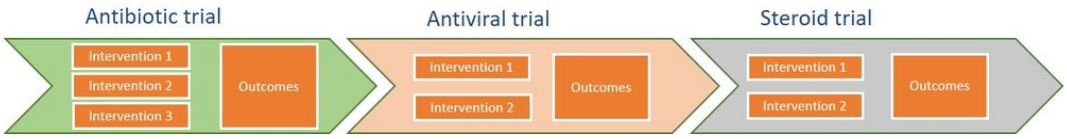
Sample plates banked for further metabolic profiling analysis

APPENDIX A: Supported clinical trials

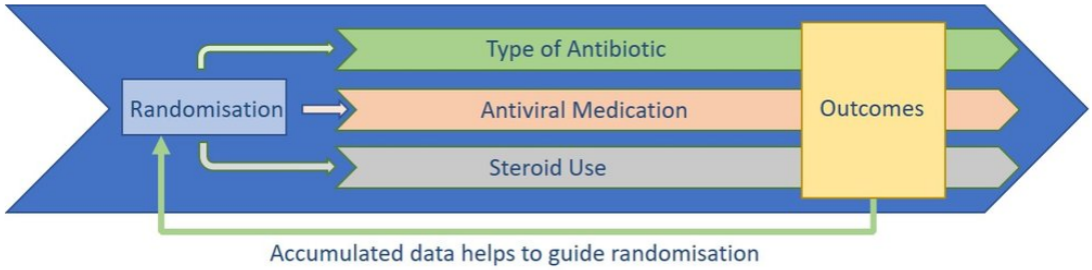
The CRR platform for data collection and biobanking in line with the WHO ISARIC protocol will form a foundation to facilitate and enable research across WA. Examples are listed below of key international and Australian trials. At present there are 47 proposals in WA most of which can be based off the CRR, reducing costs and enabling more researchers access: -

REMAP CAP https://www.remapcap.org/

REMAP-CAP REMAP, a Randomised, Embedded, Multifactorial, Adaptive Platform trial. The broad objective of REMAP is, to determine and continuously update the optimal set of treatments for community-acquired pneumonia. In a traditional clinical trial, selected patients are allocated to receive one treatment from a short list of alternatives (typically one or two). Different questions are tested sequentially.



Patients who are eligible for participation in REMAP-CAP will be randomised to receive one intervention in each of one or more categories of treatment ("domains"). These interventions can be tested simultaneously. Information from patients already participating in the study can also be used to help guide the treatment of new patients joining the study. Most trials are not able to do this.



COVID-19 Domains

All participating sites will be able to participate in two existing domains that have relevance to the treatment of patients with severe CAP resulting from coronavirus. These are:

- Evaluation of prolonged macrolide therapy, as a modulator of immune function
- Evaluation of alternative corticosteroid strategies (no corticosteroids, low dose hydrocortisone for 7 days, or hydrocortisone while the patient is in septic shock)

In addition, two new domains specific for COVID-19 have now been granted ethical approval:

- Antiviral therapy: evaluating no antiviral therapy for COVID-19 (and no placebo), and lopinavir/ritonavir (Kaletra)
- Immune Modulation therapy: evaluating no immune-modulating therapy for COVID-19 (and no placebo), Interferon-beta-1a, and interleukin-1 receptor antagonist (Anakinra)

In contrast to a conventional trial, the adaptive design of a REMAP has a number of benefits: Ambiguous results are avoided. Answers to a question can be concluded when sufficient data have accrued, rather than when a pre-specified sample size is reached. The effect of treatment options can be evaluated in pre-defined subgroups of patients (termed strata). Data that is already accrued is utilised to increase the likelihood that patients within the trial are randomised to treatments that are more likely to be beneficial. Multiple questions can be evaluated simultaneously. New questions can be substituted into the trial as initial questions are answered, meaning that the trial can be perpetual (or at least open-ended). Interactions between interventions in different domains can be evaluated

Australasian COVID-19 Trial (ASCOT)

A multi-centre clinical trial to assess clinical, virological and immunological outcomes in patients with SARS-CoV-2 infection (COVID-19) treated with lopinavir/ritonavir and/or hydroxychloroquine compared to standard of care). Protocol number: 62646

All patients will receive standard supportive therapy chosen by their doctor. This includes close monitoring, and treatments such as inhaled oxygen if needed. The ASCOT trial will randomise patients to one of four potential treatment arms

1. Hydroxychloroquine (also known as Plaquenil) - two tablets (400mg) three times a day for 3 days, and then one tablet (200mg) twice a day for 7 days
2. Lopinavir 400mg/ritonavir 100mg, one tablet twice a day for 10 days.
3. Both of the above drugs.
4. Standard supportive therapy.

The important aspect about ASCOT is that the recruitment, testing and sampling can be based on and incorporated by the proposed CRR ISARIC database:

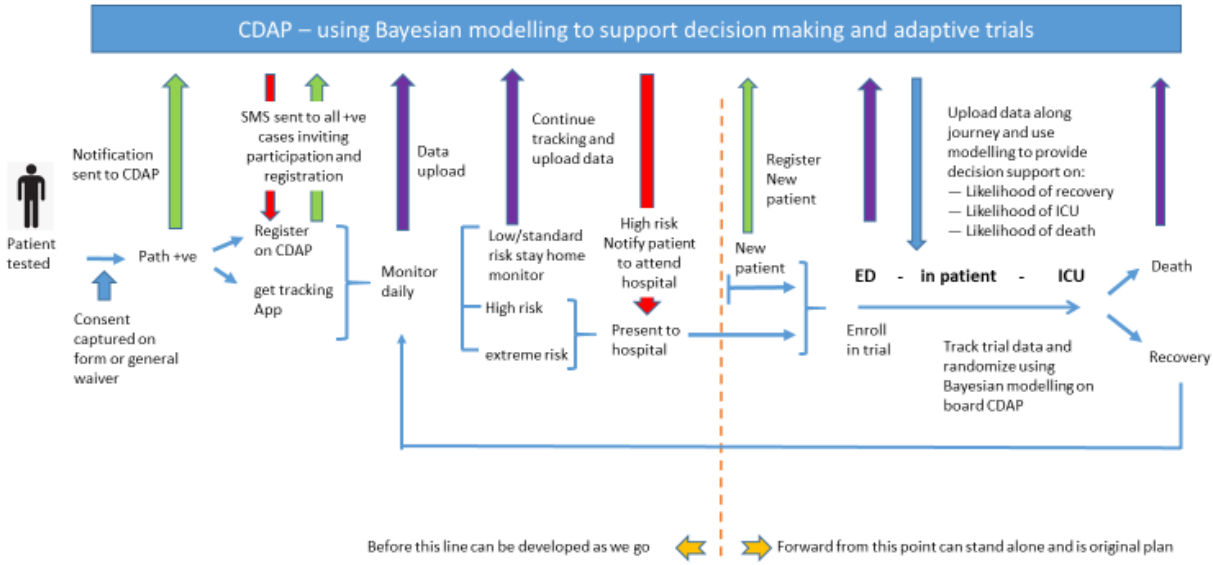
Additional testing is covered within the existing ethics and governance allowing for rapid set up and efficienct running of the trial:

Nose and throat swabs on days 1, 3, and 7 of the study
Electrocardiogram (ECG) at days 1, 2 and 7 of the study
Enhanced sampling: Daily respiratory tract swabs, rectal swabs at days 1, 4, and 7, and additional blood on days 1, 3, 7, 15, 21 and 28 to be stored for potential future research about COVID-19 and related conditions.

The Clinical Data and Analytics Platform (CDAP)

There is a critical need for health systems to be able to utilise their digitised health data for improving patient care. The Clinical Data and Analytics Platform (CDAP) will support the Australian response to the COVID-19 pandemic by creating a means to capture a broad range of **clinical data and patient reported data based on the ISARIC protocol** spanning the entire patient journey from diagnosis through management and into long term follow up.

Pending consent changes under the guardianship review and appropriate overnance authority the CRR would be well placed to digitalise and automated collaboration to the CDAP:



APPENDIX B

Role of Senior Medical Students Letter in press @MJA

The current COVID-19 crisis, unprecedented in living memory, warrants decisive action to stifle rising infections and mortalities. This statement offers a medical student perspective as to our potential role, competencies, and risks to students associated with providing a contribution to the COVID-19 response.

On March 11th 2020, the WHO declared COVID-19 a pandemic. Australia has enacted public health measures to reduce the number and severity of cases[1]. These measures, alongside disease burden, profoundly impact the healthcare system. It is unclear what the place of medical students in the COVID-19 response is.

The gravity of the COVID-19 crisis has led governments to take drastic measures. Over 10,000 Italian final year students have had graduation expedited to supplement the overburdened workforce[2]. In the UK, the Medical Schools Council has encouraged prioritising qualification of final year students to support the over-encumbered National Health Service[2].

The Medical Deans of Australia and New Zealand recognise the value of final year medical students, releasing a statement outlining appropriate roles[3]. These involve routine aspects of care independent of the COVID-19 response, in various clinical setting that students are already familiar with. Moreover, with clinical placements being disrupted, senior students may gain valuable practical exposure aligning with course requirements. Considering the noted mental health effects of COVID-19[4], student contributions may relieve burden on professional staff while alleviating any sense of helplessness, improving the mental wellbeing of students and staff alike. Importantly, medicine embodies altruism and humanity, with many students preferencing this vocation for these moral reasons. If imminent doctors feel impassioned to contribute, it is just to respect this desire as the system would, had COVID-19 surfaced mere months later.

Involving students, however, is not without risk. With the reported asymptomatic infectious period, expanding the workforce elevates infection risk. Exposure to COVID-19 patients should thus be minimal. Furthermore, the risk of litigation is pertinent as students are less experienced than professional staff. Responsibilities should be within capabilities, under supervision and institutional medico-legal protection. Lastly, additional work hours may impede formal medical education; academic penalties should not be levied with due acknowledgment of on-the-job learning and accessibility of course materials should be maximised. Indeed, medical student involvement should be implemented following principles developed by key stakeholders[3,5]. Extraordinary times call for extraordinary measures. With appropriate legal, operational and training safeguards, senior medical students have a role in the COVD-19 response if they desire.

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Australian Medical Council's 'Standards for Assessment and Accreditation of Primary Medical Programs':

1. Science and scholarship: the medical graduate as scientist and scholar

1.2 Apply core and medical and scientific knowledge to individual patients, populations and health systems.

1.5 Apply knowledge of common scientific methods to formulate relevant research questions and select applicable study designs.

3. Health and society: the medical graduate as a health advocate

3.1 Accept responsibility to protect and advance the health and wellbeing of individuals, communities and populations.

3.3 Communicate effectively in wider roles including health advocacy, teaching, assessing and appraising.

3.5 Explain and evaluate common population health screening and prevention approaches, including the use of technology for surveillance and monitoring of the health status of populations. Explain environmental and lifestyle health risks and advocate for healthy lifestyle choices.

3.6 Describe a systems approach to improving the quality and safety of health care.

4. Professionalism and leadership: the medical graduate as a professional and leader

4.2 Demonstrate professional values including commitment to high quality clinical standards, compassion, empathy and respect for all patients. Demonstrate the qualities of integrity, honesty, leadership and partnership to patients, the profession and society.

4.3 Describe the principles and practice of professionalism and leadership in healthcare.

Collaborative outputs & authorship

The CRR will be propose a collaborative authorship agreement. In principle, the CRR is a collaborations and all people offering a major contribution will be included in authorship '*on behalf of the Western Australian COVID Research Response'.*

Group authorship: collaborators
Groups who wish individuals to be credited with authorship should provide a list, together with a statement that the individuals are collaborators of the study. The names of group members will then be published under the heading: collaborators. Each collaborator will be tagged individually, so that they will be picked up by PubMed and credited accordingly. If there is a long list of collaborators, it may be published online only.

Kohrt BA, Mistry AS, Anand N, *et al*. Health research in humanitarian crises: an urgent global imperative. *BMJ Global Health* 2019;4:e001870. doi:10.1136/bmjgh-2019-001870

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Computing & Bioinformatics

The National Computational Infrastructure (NCI) and Pawsey Supercomputing Centre (Pawsey) are joining efforts to offer additional computation and data resources to support the national and international research community to acquire, process, analyse, store and share data supporting COVID-19 research.

https://pawsey.org.au/covid19-accelerated-access/