

EDICT - EARLY DIGITAL/DRUG INTERVENTION FOR COVID-19 THERAPY ('EDICT')

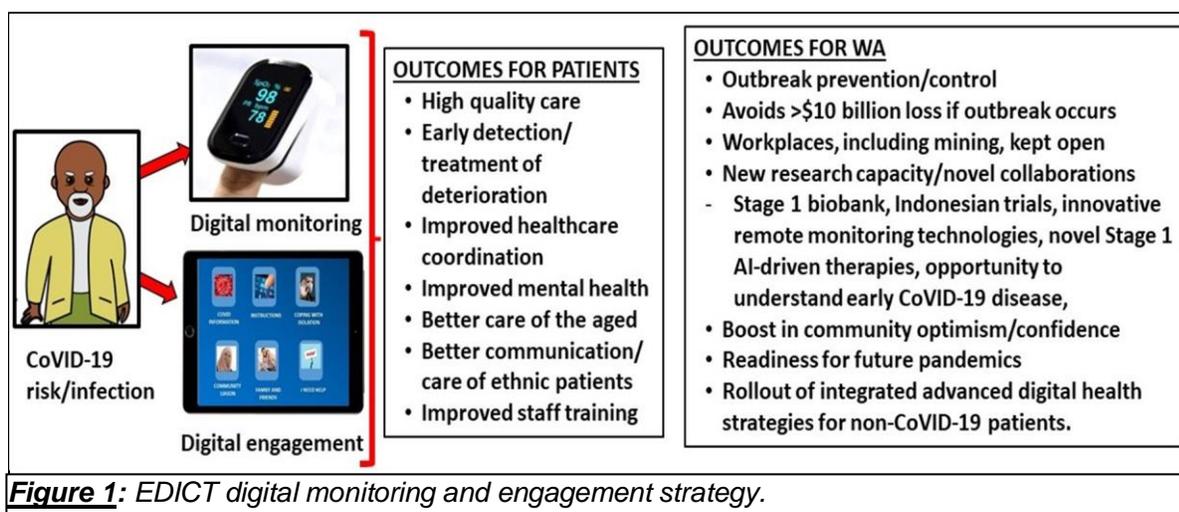


Figure 1: EDICT digital monitoring and engagement strategy.

CoVID-19 results in **strict isolation** for those at risk/infected. The EDICT project used digital (electronic) methods of communication to overcome the challenges of isolation by sending clinical information **FROM** those isolated to health care staff ('digital monitoring') to improve their clinical care, and by sending helpful/caring information from healthcare professionals **TO** those in isolation ('digital engagement'). EDICT will also study mental health and a pilot study of blood/viral changes in those in isolation.

EDICT involves a diverse collaborative network of WA leaders across health, industry, police, laboratory, government, community and consumer groups with a special focus on:

- those in quarantine or in isolation
- ethnic communities (particularly at risk of outbreaks)
- aged care facilities (most impacted)

What technologies will EDICT develop, deploy and evaluate?

Digital monitoring provides contactless, remote monitoring of validated clinical parameters for patients and those at risk who are in strict isolation.

Digital engagement is the provision of information and mental health support in an ethnically appropriate and age-specific digital way.

How will EDICT improve the health care of COVID-19 patients?

- Better monitoring of symptoms and vital signs, including early deterioration
- Improved coordination of health care providers with other state services
- More effective and culturally-appropriate education/communication about the disease
- Understanding/reducing psychological/psychiatric challenges of isolation/COVID-19

EDICT will help reduce/prevent outbreaks

'Make no mistake. The biggest threat to Western Australia is a second wave of coronavirus'

Mark McGowan. WA Premier¹

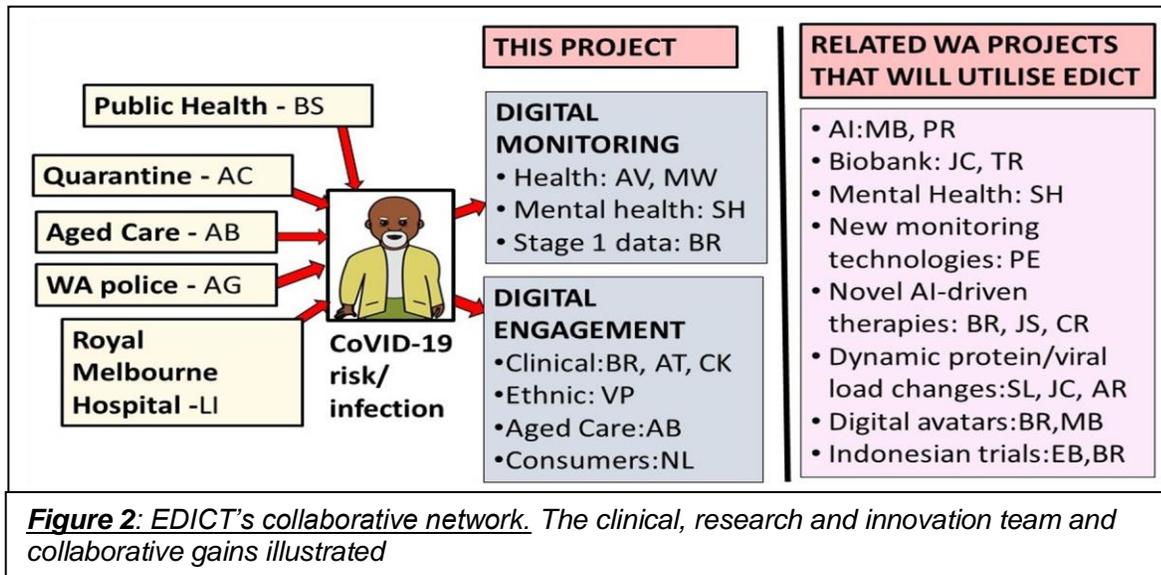
An uncontrolled outbreak will have major health, economic (>\$1b/wk) and social effects so must be avoided.

EDICT will improve

- engagement with ethnic communities (e.g. to avoid what happened in Melbourne)
“Ethnic community leaders say cultural confusion played a role in the latest outbreak².”
- mental health challenges of isolation
- training of security staff (an outbreak risk if not briefed well)³

EDICT will also help create a strong collaborative/capacity building platform (Fig 2)

- Stage 1 clinical COVID-19 data/biospecimens for sharing
- Novel stage 1 CoVID-19 therapy trials
- Artificial intelligence (AI) collaborations



Sustained improvements in digital health care of non-CoVID-19 patients

EDICT will initially be trialled on relevant non-COVID pulmonary patients (CF) and team members AT, BR, CK, LI have the clinical knowledge, experience and roles to rapidly apply the technology to these and other pulmonary diseases.

EDICT will also generate preparedness for future non COVID-19 pandemics

Why will this program succeed? We have:

- the necessary skills and experience
- access to all required patients/at risk individuals
- a well-established collaborative team
- enormous experience of digital home monitoring (>1500 non-COVID patients via Emyria) and monitoring of quarantined individuals (via collaborative partner GenVis) – no-one else in WA has this.
- research credentials at the top level (1,048 papers, 69,427 citations)
- a defined strategy for co-ordination, planning and execution
- strong governance

Threats/risks

The main threat is inadequate funding (see under Budget). There is no alternative funding for this project. Without this sort of program to complement public health WA is at risk of not being able to optimally care for isolated patients nor control inevitable outbreaks.

RELEVANCE AND SIGNIFICANCE for Research and Innovation into CoVID-19.

EDICT program has broad significance for CoVID-19 worldwide – the pandemic has surged past 35 million infections with >1 million deaths⁴. In WA, we have had an effective public health response but the risk of a Melbourne-type outbreak remains and this grant provides a platform of preparedness so that those risks can be mitigated.

EDICT's innovative nature and the widely applicable and multidisciplinary digital platform we create will not only generate novel, dynamic research approaches and enhance other WA CoVID-19 research programs but will complement the state's highly effective public health, police and health planning activities.

The EDICT program is relevant and significant for WA because it will facilitate deployment and development plus collaborative studies in:

A. DIGITAL MONITORING

Patient management – The EDICT platform supports research into the optimal clinical care of CoVID-19 outpatients who are in isolation by helping deploy and validate novel methods for rapidly capturing and sharing the most relevant clinical information with health workers. EDICT can help identify those who need intervention earlier as well as facilitate response coordination across ***multidisciplinary teams*** of existing healthcare providers, public health and police.

Outbreak prevention/control – EDICT will generate research and implementation strategies to reduce WA's vulnerability to the importation of CoVID-19 by sea, air and land.

B. DIGITAL ENGAGEMENT

Engagement with ethnic communities. EDICT's program will develop strategies for improved communication with each ethnic community. This is highly relevant to WA because English is not the language spoken at home in 17.5% of WA homes i.e. by around 433,000 people (ABS).

Improved care of the aged. EDICT's collaboration with Bethanie, WA's largest aged care provider, will develop new research approaches and improve the clinical care of the aged.

Training of staff (healthcare and security). We will extend the reach of our engagement to include staff such as aged care workers (~30% get COVID-19 infected, cross infect and require replacement) and security staff (lack of knowledge ignorance of COVID-19 has contributed to outbreaks) – our program will compare/evaluate and implement the optimal approaches to succeed in this task.

C. MENTAL WELL-BEING

EDICT has a special focus on mental health, a major challenge in COVID-19⁵. Our digital monitoring will study/identify levels and types of mental stress in those in isolation/quarantine and the digital engagement program will study ways of optimally engagement to reduce feelings such as loneliness, anger, depression and anxiety, including those in aged and residential care as above. It will also obtain ongoing detailed mental health wellbeing data.

A. A BROAD COLLABORATIVE PLATFORM FOR THE STUDY OF STAGE-1 COVID-19

WA's low CoVID-19 transmission rates means we have the 'breathing space' to fund and foster a collaborative group to study the early stages of CoVID-19; EDICT will facilitate integration of information with multidisciplinary teams of existing healthcare providers, public health jurisdictions and police and create a platform for many other important research projects in WA and elsewhere. These are summarized in Figure 2 and listed in more detail below. Although these projects are not feasible within the budget of this study, EDICT will underpin those studies.

GAPS AND CHALLENGES

The EDICT strategies listed above address specific gaps. In brief these gaps related to: ***controlling outbreaks*** (better information/monitoring resources are required to reduce outbreaks); ***challenges in ethnic communities*** (many outbreaks, including the recent

Melbourne outbreak, occur in ethnic communities where public health messages can be difficult to deliver effectively due to language and cultural barriers²; **challenges in aged care** (they are hardest hit⁴ but isolation causes cognitive and emotional decline, with long lasting effects); **Stage 1 COVID-19 patient management** (the high level of digital monitoring required to improve the clinical care of isolated COVID-19 outpatients has not been developed and proven); **mental well-being** (those in isolation or quarantine often experience loneliness, depression, abandonment, uncertainty, depression and frustration⁶). The short and long term mental health impact of COVID 19 infection remains poorly understood; **workplace functioning** (to keep workplaces/mining activities functioning we need new, advanced, accurate and well validated digital monitoring and screening services – not just for infection risk but mental health also); **COVID-19 collaboration in WA** (WA's low CoVID-19 transmission rates means we have the 'breathing space' to fund and foster a collaborative group to study the early stages of CoVID-19); **understanding early stage COVID-19 disease** (because Stage 1 CoVID-19 patients are in strict isolation, few if any studies of the daily dynamics of their blood cytokine/chemokine patterns, their viral load and their symptoms and signs have been possible. We also need to find ways of using this information); **finding a therapy that works** (drug trials have largely failed in Stage 2 but Stage 1 CoVID-19 patients, who should respond better to therapy, are rarely studied because it is neither safe nor ethical to conduct trials in isolated patients (>98% of COVID-19 trials are on inpatients). Accurate, sophisticated monitoring is essential); **the dynamics of biomarker/viral load changes in early COVID-19 is not understood** (there are many CoVID-19 biobanks relating to Stages 2/3 of the disease (inpatients) but not from Stage 1 patients. WA has an opportunity to create this; **new remote monitoring technologies need to be tested** (new technologies for digital monitoring have been/are being developed and we need methods to rapidly deploy, test and validate these technologies in CoVID-19 so that we can rapidly respond to the next pandemic); **advancing the use of digital technologies for other non-COVID-19 diseases** (digital health will be a crucial component of future health care in all jurisdictions⁷ yet new technologies have not been well studied, including using advanced AI)

EDICT will deliver on most of **WA's Sustainable Health Review Strategies**⁸ as follows: **#1 - Commit and collaborate to address major public health issues (COVID-19), #2 Improve mental health outcomes (Aims 2/3), #4 - Person-centred, equitable, seamless access (digital health), #6 Invest in digital healthcare and use data wisely (this whole project), #7 - Culture and workforce to support new models of care and #8 - Innovate for sustainability.**

Anticipated specific contribution and benefits to WA in research/innovative health studies.

Health – we will identify optimal health monitoring strategies and features predicting deterioration This will be particularly impactful in our two key focus groups, aged care and ethnic communities

Outbreak control. The combination of close engagement with individuals in isolation/quarantine, ethnic communities, aged care facilities, WA Police and public health underpins our research platform to reduce the risk of Melbourne-type outbreaks.

Mental health benefits. EDICT is also an ideal research platform to study the optimal methods of engagement with individuals to influence their mental well-being.

Digital health capabilities. COVID-19 has given us an opportunity to develop sophisticated world-class digital health/AI capabilities for patients in the WA community and researchers.

Broader application: One of the strengths of this program is its **ready applicability to future digital health care of other diseases.** Indeed, part of this project is the trialling of some of the new monitoring approaches in patients at risk of acute on chronic respiratory disease e.g. cystic fibrosis (CF). So, this project will impact on

- a. Skill acquisition in the field of digital health in WA, adding value to the Hospital-in-the-Home programs and other outpatient programs that already exist.
 - b. The contactless monitoring of many pulmonary diseases such as CF, COPD, interstitial lung disease, brittle asthma as well as non-pulmonary diseases, including cancer
 - c. EDICT will also increase the readiness of WA to deal with future viral pandemics.
- EDICT is a niche program. No other group has this combination of sophisticated monitoring technology combined with patient engagement plus the required advanced algorithm-based logic to support this high level of clinical monitoring of early-phase disease

How this project will help build WA's research and innovation environment

EDICT will help build WA's research and innovation infrastructure by generating digital infrastructural platforms that will facilitate ongoing research and implementation of contactless, direct remote clinical monitoring of individuals at risk of/suffering from a number of non-COVID-19 diseases to improve WA's capacity to deliver high level outpatient care of its population.

EDICT's digital engagement strategies will generate new, ongoing information and methods to study ways of delivering information to ethnically diverse and aged non-COVID-19 populations. This will include the empathy styles discovered by EDICT to be most effective in improving/maintaining patient mental health. These strategies will also be useful as a platform for staff training.

The dynamic (daily) blood and viral load microsampling in early disease will add a unique resource to existing CoVID-19 biobanks in WA

EDICT's AI analytical collaborators will be available to apply these advanced methods to other diseases, including discovery and trialling of novel therapeutic strategies⁹

Driving COVID-19 collaboration in WA through EDICT's capabilities (Fig 2).

Not only will this project be collaborative across many institutions, disciplines and individuals, it will create a platform for additional collaborations in W.A. beyond that which are listed in the grant (Figure 2). This includes:

Understanding early stage COVID-19 disease – EDICT will provide a means of collecting samples to study the daily dynamics of blood cytokine/chemokine patterns and viral load (JC,AR,TR,SL,MB). **AI-driven data analysis.** EDICT will generate data that will facilitate AI analysis to identify clinically relevant symptom/vital sign features that can predict deterioration or recovery. This will open the door to identifying CoVID-19 subtype patterns that will permit more personalised therapeutic approaches as well as AI-backed clinical decision support tools (MW,MB,JS). **Workplace functioning.** EDICT will generate data related to optimal means of keeping workplaces open by the early and rapid detection of disease risk, prediction of severe CoVID-19 and ultimately by turning COVID-19 into a 'mild flu' (BR,JS). **New remote monitoring technologies** – EDICT will test and compare new digital monitoring technologies that have never before applied to CoVID-19 patients (MW,AV,PE). **Drug trials in early Stage 1 disease** – EDICT will provide a means of conducting clinical trials in isolated in Stage 1 CoVID-19 patients with the goal of 'putting a finger in the dike' to stop disease progression at the very stage when it is predicted to be most reversible. Vaccines may not be effective and it has been stated that 'Australia needs a plan B'¹⁰. We have an AI-driven drug trial ready to start (BR,JS,RA). EDICT will generate a means of studying and improving our capacity to rapidly respond to **future similar viral pandemics**-by delineating the different features of early viral pneumonias and, combined with our AI-drug prediction approaches, could be rapidly mobilized to undertake trials in any similar viral pandemic event in the future. EDICT also provides a platform to improve our capacity to study and deliver **remote monitoring of other non-COVID-19 diseases** (AT,BR,CK). Our advanced digital health approaches will be

important components of future health care and WA, with its vast area, will especially benefit from improved digital contactless methods of monitoring diseases.

Specific research outcomes from **digital monitoring** will include home monitoring technology development, a Stage 1 clinical data base (symptoms, vital signs) linked to outcomes, alert and prediction algorithms using machine learning; our **digital engagement** platform will generate best-practice guidelines for delivering effective, engaging and culturally appropriate public health information and education. Additional research outcomes will include high impact publications, applications for peer reviewed grants and further development of collaborative teams in this field. Additional research outcomes will include the training of doctors, allied health workers, Aged care staff, ethnic community leaders Consumers and others in home monitoring and engagement in COVID-19 and other diseases.

Overall the EDICT program is WA-led and in addition to fostering collaboration between many groups in WA [Figure 2]. It will also be a platform for collaboration with others in Australia and internationally, including in developing nations in our neighbourhood who are most at risk of multiple devastating waves of CoVID-19 but who don't have the health or wealth do deal with them. EDICT's broad collaborative network will link with existing WA CoVID-19 research groups such as WAHTN's COVID-19 network plus the CRR (CoVID-19 Research Response) through CI Richards.

This project includes broad collaboration across disciplines such as pulmonary medicine, infectious disease, public health, community medicine, psychiatry, consumers, ethnic communities, aged care facilities, WA Police, drug trial development, artificial intelligence and biobanking.

The institutions in WA involved in this collaboration include the Institute for Respiratory Health (UWA), Sir Charles Gardner Hospital (SCGH), Royal Perth Hospital, Emyria Inc. GenVis, The Health Consumers Council (HCC), the Ethnic Community Council of WA (ECCWA), Bethanie Aged Care, the SCGH/UWAQ Department of Psychiatry, North and East Metropolitan Area Health Services, GP services, WA Police, GenViz, Proteomics International. Other institutions involved, particularly in the collaborations that will flow from this project, include Stanford University, Imperial College London, University of Indonesia, Doherty Institute, Monash, Oxford and the WHO (see collaborator list above).

The services and processes in this project will impact broadly on WA health. These will range from public health engagement with at risk and infected individuals, multidisciplinary responses to infected patients, close liaison with pulmonary departments for early intervention of patients whose home monitoring shows signs of early deterioration, the further development of digital health and the capacity to rapidly respond to any similar health challenge in the future, staff training and digital health and COVID-19 (which includes security staff, aged care service staff and individuals of different ethnic backgrounds).

This project, because of its digital nature, could be rapidly scaled up for use throughout the state, including rural areas, and in different jurisdictions, aged and residential care facilities, additional ethnic communities and indeed, once established and optimised, can be readily scaled up for use in other states and internationally. Health economic analysis would undertake before such expansion.

An individual's journey with EDICT: A COVID-19 positive individual will be contacted by a team member, consented, receive the monitoring technology and be trained by phone and

digital instruction in a culturally and age-appropriate way. Their daily data will be sent via a secure central dashboard and monitored by Emyria's clinical team. If an alert is triggered or the patient is unwell, Emyria's clinical team will liaise with either our respiratory specialist collaborators (for CF/COPD patients), WA Public Health (for COVID or quarantined individuals) or mental health services, or provide a telehealth consult, supportive monitoring or further testing as clinically indicated. Non English speaker patients/contacts will have all information delivered in their specific language within 24 hours.

Patient acquisition

a. CF outpatients: In order to deploy and validate the remote monitoring equipment we will first study non-isolated pulmonary patients at risk of disease progression. The SCGH pulmonary clinics are the state centre for adults with CF in WA. The centre currently provides care for >180 adults with CF. 20 suitable patients with CF with a high likelihood of requiring home intravenous antibiotics will be prospectively recruited into the current study as a control validation group.

b. COVID-19: These will be obtained via the WA Public health team who are the key players informing all newly diagnosed COVID 19 patients of their positive test result. They also routinely consent patients over the phone for future contact by relevant COVID 19 research teams during the initial phone conversation. Uptake is 70%+ of all COVID-19 positive patients. Data sharing between Public health and EDICT will be seamless once funded and all HREC and Governance approvals are obtained. The daily automated list of newly diagnosed COVID-19 patients (who have consented to be contacted) will be shared to our clinical trials team to enable rapid patient contact, recruitment, screening and enrolment into the EDICT platform. Our target is 100 COVID-19 positive individuals over two years. That total is assured because we have named collaborators in other jurisdictions who can provide cases (eg. Prof LI, RMH).

c. Control individuals: Will be matched and chosen in numbers equal to the test cohorts. COVID-19-free aged care patients from Bethanie and ethnically diverse individuals from pulmonary SCGH clinics will be invited to participate. They will not receive the interventions to enable additional comparison/quantification of differences in the tested parameters.

Digital Monitoring

In order to understand the ease of deployment, clinical utility and validity of EDICT's smartphone-only symptom and vital sign measurement technology compared with standard remote vital sign measuring hardware, we will deploy EDICT's digital health platform, digital engagement strategies and measurably effective communication tools amongst 3 core groups: (1) a population of remotely managed, vulnerable and ethnically diverse CF/COPD and COVID-19 patients, (2) A primary care team coordinating care amongst public health and other services and; (3) Clinical researchers who will study and improve the effectiveness of the system.

Remote Data Capture: The digital health platform will capture and monitor symptoms as well as measurements of the major physiological characteristics of respiratory exacerbation: fever (temperature is recorded); breathing difficulties (blood oxygen levels and breathing rate); as well as heart rate and, in selected cases, lung function via spirometry. Such information adds objective data to the subjective data obtained from protocolised, symptom-only follow up. The monitoring program will run for 2 weeks per participant. Data are continuously uploaded to a secure cloud service that allows the output to be viewed by a clinical team.

Smartphone monitoring app: All participants will download the **Hallo app** (iOS or android versions already live) which has been built by one of our technical collaborating partners GenVis. A version of the smartphone app is already in the market and operated by WA Police and WA Health as G2G Now. The app collects daily health updates from people who have entered WA and are subject to a quarantine direction. It allows users to register COVID tests

and results and would be used to capture any additional data that can then be assessed and used for research purposes.

This smartphone app will deliver reminders and participants will be invited to complete a short daily symptom questionnaire. For a sub-set of users with modern smartphones, **Hallo** will link to another app - **Openly** - to capture heart rate and heart rate variability via a contactless, smartphone-only technology. **Remote electronic monitoring devices:** All participants will be mailed or provided a kit containing a simple wearable device capable of providing continuous measurements of vital signs (body temperature, respiration, pulse rate) along with blood oxygen levels (Philips wearable biosensor BX100, or equivalent). **Spirometry:** CF Participants are provided with a hand-held spirometer (Spirohome, Bird Healthcare) and instructed to perform daily spirometry during the study. **Temperature** will be captured by take-home devices and self-recorded into the **Hallo** app.

Patient Management: Emyria's clinical team will monitor all alerts that are generated on symptom responses or measurement excursions outside of accepted values via a dashboard and coordinate with SCGH Respiratory team and SCGH hospital-in-the-home team as required.

Evaluation: An estimated 80% of COVID-positive individuals⁴ show no symptoms in the early stages of disease. It is therefore desirable to understand whether there are objective clinical signs that can act as markers of disease evolution or clinical deterioration. This information can help resource-limited public health teams better manage isolating individuals and also help increase the pre-test probability of testing programs.

Encouragingly, it has been shown in two recent studies, that an individual's vital signs can act as an early warning of disease progression. In a study of 1,181 subjects wearing a Fitbit device¹, it was shown that increases in Heart Rate (HR) and Respiratory Rate (RR) alongside decreases in Heart Rate Variability (HRV), preceded symptomatic awareness of illness by 4 days. Further, another study using the Whoop device, corroborated this finding. In a study of 271 individuals, increases in respiratory rate were helpful in predicting 20% of COVID-19 positive cases in the two days prior to symptom onset. In order to validate these findings we will conduct frequent analysis of all collected data (symptom trends, vital sign changes and COVID-19 status) to support the development of clinical decision support tools that can help stratify future patient populations and identify signs of deterioration earlier. In addition, an analysis of measurement concordance will be performed between the hardware captured vital sign measurements and the contactless vital sign measures using mean error calculation and Bland Altman comparisons.

Digital Engagement: In order to improve communication with the patients we will assess improvements in information acquisition, psychological changes and clarity of instruction in the above target groups compared to matched control groups who do not use the technology at all. We will assess how EDICT helps patients:

- better engage with ethnic communities and establish, via our collaborators in the ECCWA, HCC and our medical/public health COVID-19 collaborators, a development program to identify the best strategies for COVID-19 digital communication (content, style, frequency, methods eg. web, social media, email, and strategy e.g. via community leaders, religious leaders, key individuals, ethnic media etc. generate and test this digital engagement material in English subtitled in the five most common non-English languages and spoken in these five

different languages. evaluate the above, identify strengths and weaknesses of our test strategies and iteratively modify and retest these strategies until we have optimised these digital methods.

- better engage with those in aged care we will follow a similar procedure with our aged and residential care collaborators (AB) plus our medical/public health COVID-19 collaborators. This will include the development and testing of novel digital software to identify that which is optimal for the aged (Figure 3 is an example). The majority of aged care residents are, since COVID-19, able to engage with simple digital technologies. A detailed analysis will then be conducted in 30 non-COVID-19 individuals, 30 each with COVID-19 at ages 65-74, 75-84 and >85

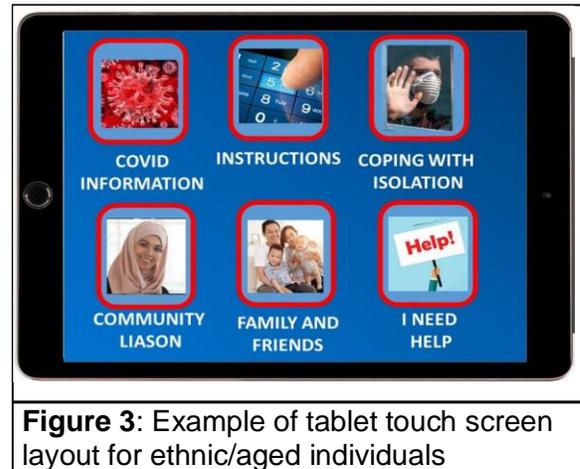


Figure 3: Example of tablet touch screen layout for ethnic/aged individuals

- we will also modify these digital assets to evaluate their capacity to improve staff training (Bethanie aged care and quarantine security staff)

Psychological of COVID-19: The EDICT Platform will further develop the capacity for remote psychology screening using electronic questionnaires and telecommunication technologies. We have built on existing questionnaires to gather data more related to COVID cohort This will facilitate systematic research to address important COVID-19 related mental health priorities. Each participant will fill in a weekly electronic screening questionnaire isomg tej smartphone App addressing demographics, family support, household stressors/stress, medical support, exhaustion/fatigue, general Health, sleep patterns as a result of COVID, Somatic Symptom Scale, stigma analysis, media exposure, acute stress (Impact of Events Scale), depression & anxiety (PHQ-9 and GAD-7). The survey will provide a forum for COVID-19 patients in home isolation to describe any key concerns, stressors/supports not covered in the survey. This survey will also provide information on contact details of Lifeline support, acute community mental health services and local emergency department.

This will build a standardised, longitudinally repeated neuropsychological data base in all patients with COVID 19 (from diagnosis to recovery) in a clinically, ethnically and geographically inclusive population and identify effective short and long term interventional strategies to support and prevent psychiatric complications in patients with COVID-19 infection

Collaborative platform: This is described above. Briefly, a successful EDICT program will underpin a number of collaborative programs. In this particular study we will undertake some pilot studies. **Stage 1 microsampling.** Participants will use capillary blood collection and nasal swab kits which contain all of the necessary equipment, and receive instruction. Second-daily samples will be taken, stored at 4° and collected weekly by the team. In some cases (e.g. quarantine) Clinipath will collect these samples on contract. Preliminary studies will include measurement of cytokines, using a 65-plex assay, in sequential these samples and an unsupervised proteomics approach to validate a biomarker discovery platform. Viral load will be assayed by Pathwest. This will be conducted in collaboration with CI TR, linked to the WAHTN COVID19 Research Collaboration, CRR and the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC), a is a global initiative to share data. Preliminary **AI analysis** of the accumulated data will be undertaken by our CIs (MB, PR) as described above.

Specific team skills: EDICT has experience in digital health monitoring (MW, AV; >1500 patients), respiratory medicine (BR, AT, CK, LI), public health and COVID-19 quarantine (BS, AC,AG), aged care (AB), ethnic community engagement (VP), consumer

engagement (NL), immunology (BR,AR), COVID-19 care 9ZT, CK, LI, EB), biobanking (TR,JC), AI-driven data analysis and drug design (MB,JS,RA,PR).

The specific skill sets and roles of each of the Chief Investigators are listed above in Section 2(ii).