**Protocol**

The protocol (project description) is to be submitted with the HREA form to the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC)

The HREA form ensures your project complies with the ethical considerations for research, outlined in the National Statement on the Ethical Conduct in Human Research.

The protocol provides the SAC HREC with the design, objectives, methodology and rationale on how the research project will be conducted.

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| **Project Title: Cost Effective Improvements in Mental Illness using Pharmacogenetics** |

# Project team

The person listed as the Chief Investigator / Principal Investigator is responsible for the conduct of the research and listed study staff until completion of the project.

A student cannot be listed as the Coordinating Principal Investigator or Principal Investigator

Explain the role in the study that each Investigator will perform at each site and clearly state whether Investigators will work on or off the relevant public LHN site(s).

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| Name: Professor Malcolm Battersby | |
| Institutional affiliation: Flinders University of South Australia | |
| What is the position of this person on the research project? Chief Investigator, Clinical Psychiatrist | |
| Prof. Battersby is a clinical academic, Head of Psychiatry at Flinders University and is located in Margaret Tobin Centre, the site of psychiatric intensive and acute care units. Prof. Battersby will direct clinical staff and other research team members.  Does this person have a current Good Clinical Practice certificate? ☒ Yes / ☐ No | |
| Department and department address: Margaret Tobin Centre, College of Medicine and Public Health, Flinders Medical Centre, Bedford, Park, SA 5042 | |
| Contact details: a Health or University email address is preferred  ☒ I am the contact person for this project | Phone: +61 8 84042314  Email: [malcolm.battersby@flinders.edu.au](mailto:malcolm.battersby@flinders.edu.au) |
| Name: Professor Michael Sorich | |
| Institutional affiliation: Flinders University of South Australia | |
| What is the position of this person on the research project? Clinical Pharmacologist | |

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| Michael Sorich is Professor of Clinical Pharmacology and Head of the Precision Medicines Research Group at Flinders University. He is a pharmacists and biostatistician, with very extensive experience in the evaluation and modelling (statistical, pharmacokinetic, machine- learning, cost-effectiveness) of precision medicine biomarkers for their value in improving therapeutic decision making. Prof. Sorich will oversee the precision medicine recommendations based on patient genotypes.  Does this person have a current Good Clinical Practice certificate? ☒ Yes / ☐ No | |
| Department and department address: College of Medicine and Public Health, Flinders Medical Centre, Bedford, Park, SA 5042 | |
| Contact details: a Health or University email address must be used | Phone: +61 8 82046682  Email: [michael.sorich@flinders.edu.au](mailto:michael.sorich@flinders.edu.au) |

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| Name: Professor Tarun Bastiampillai | |
| Institutional affiliation: Flinders University of South Australia | |
| What is the position of this person on the research project? Clinical Analytics & Translation | |
| Professor Bastiampillai is a clinical psychiatrist and university academic. He has significant experience in clinical analytics currently serving as the SA Department of Health and Wellbeing Clinical analytics advisor for acute healthcare analysis. Prof. Bastiampillai will be a member of the Digital Hub and will lead the clinical interpretation of data monitoring and prescribing by doctors and medication adherence of patients in the trial. Prof.Bastiampillai has expertise in translation of trial evidence into clinical service delivery.  Does this person have a current Good Clinical Practice certificate? ☒ Yes / ☐ No | |
| Department and department address: College of Medicine and Public Health, Flinders Medical Centre, Bedford, Park, SA 5042 | |
| Contact details: a Health or University email address must be used | Phone: Click here to enter text.  Email: [tarun.bastiampillai@flinders.edu.au](mailto:tarun.bastiampillai@flinders.edu.au) |

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| Name: Dr Martin Lewis |
| Institutional affiliation: Flinders University of South Australia / SAHMRI |
| What is the position of this person on the research project? Neurogeneticist / DNA genotyping |
| Dr Lewis is a neurogeneticist that heads the Neuropsychiatric Laboratory at SAHMRI and is an affiliate senior lecturer in the College of Medicine and Public Health at Flinders University. Dr Lewis has expertise in the pharmacogenomics of mental health and will lead the genetics sequencing and genotyping aspects of the project. |

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| Does this person have a current Good Clinical Practice certificate? ☒ Yes / ☐ No | |
| Department and department address: Dept. Psychiatry, College of Medicine and Public Health, Flinders Medical Centre, Bedford Park, SA 5042. / Neuropsychiatric Laboratory, SAHMRI. | |
| Contact details: a Health or University email address must be used | Phone: +61 8 81284703  Email: [martin.lewis@flinders.edu.au](mailto:martin.lewis@flinders.edu.au) |

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| Name: A/Prof Niranjan Bidargaddi | | | | |
| Institutional affiliation: Flinders University of South Australia | | | | |
| What is the position of this person on the research project? Digital Mental Health Analyst | | | | |
| Niranjan Bidargaddi is the A/Prof. of Digital Health at College of Medicine and Public Health Flinders University. A/Prof Bidargaddi established the first real-time mental health registry in Australia, to monitor relapse risk of SA public mental health service clients through automated real-time analysis of Medicare claims, through which he will contribute health outcome data for trial analysis.  Does this person have a current Good Clinical Practice certificate? ☒ Yes / ☐ No | | | | |
| Department and department address: College of Medicine and Public Health, Flinders Medical Centre, Bedford, Park, SA 5042 | | | | |
| Contact details: a Health address must be used | or | FUSA | email | Phone: +61 8 72218840  Email: [niranjan.bidargaddi@flinders.edu.au](mailto:niranjan.bidargaddi@flinders.edu.au) |

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| Name: Dr Michael Musker | | | | | | | |
| Institutional affiliation: SAHMRI and Flinders University | | | | | | | |
| What is the position of this person on the research project? Mental Health Nurse | | | | | | | |
| Dr Michael Musker, PhD is a registered mental health nurse who will oversee patient assessments and maximise completion of follow-ups. Dr Musker currently chairs a mental health consumer group as part of an MRFF project on long acting injectables in mental health. Dr Musker has extensive experience chairing mental health consumer engagement groups and conducting clinical studies.  Does this person have a current Good Clinical Practice certificate? ☒ Yes / ☐ No | | | | | | | |
| Department and department address: Adelaide Nursing School, Faculty of Health and Medical Sciences. Level 3, Helen Mayo North, Frome Rd, North Tce campus, Adelaide, SA 5005. | | | | | | | |
| Contact | details: | a | Health | or | FUSA | email | Phone: +61 8 8128 4714 |

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| address must be used | Email: [michael.musker@flinders.edu.au](mailto:michael.musker@flinders.edu.au) |

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| Name: Assoc/Prof Hossein Afzali | | | | |
| Institutional affiliation: Flinders University of South Australia | | | | |
| What is the position of this person on the research project? Health Economist | | | | |
| A/Prof Afzali will conduct the economic evaluation and cost-effectiveness of pharmacogenetic- informed clinical management compared to usual care.  Does this person have a current Good Clinical Practice certificate? ☒ Yes / ☐ No | | | | |
| Department and department address: College of Medicine and Public Health, Flinders Medical Centre, Bedford, Park, SA 5042 | | | | |
| Contact details: a Health address must be used | or | FUSA | email | Phone: +61 8 74219823  Email: [hossein.afzali@flinders.edu.au](mailto:hossein.afzali@flinders.edu.au) |

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| Name: Dr David Smith | | | | |
| Institutional affiliation: Flinders University of South Australia | | | | |
| What is the position of this person on the research project? Statistician | | | | |
| Dr Smith will provide statistical analysis of patient health and service data. Statistical modelling of pharmacogenetic intervention outcomes for mental health and prescribing changes will be assessed for numerous covariates.  Does this person have a current Good Clinical Practice certificate? ☒ Yes / ☐ No | | | | |
| Department and department address: College of Medicine and Public Health, Flinders Medical Centre, Bedford, Park, SA 5042 | | | | |
| Contact details: a Health address must be used | or | FUSA | email | Phone: +61884042610  Email: [david.smith@flinders.edu.au](mailto:david.smith@flinders.edu.au) |

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| Name: Prof. Michael Baigent |
| Institutional affiliation: Flinders University of South Australia |
| What is the position of this person on the research project? Recruiting psychiatrist |
| Prof Baigent is a senior clinical academic at Flinders University/Flinders Medical Centre, and a senior specialist with the Drug and Alcohol Services South Australia. Prof Baigent is one of the Board of Directors of BeyondBlue, the National Depression Initiative.  Does this person have a current Good Clinical Practice certificate? ☒ Yes / ☐ No |

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| Department and department address: Flinders Medical Centre, Bedford, Park, | | | Psychiatry, College of Medicine and Public Health, SA 5042 | |
| Contact details: a Health address must be used | or | FUSA | email | Phone: +61 8 82045237  Email: [michael.baigent@sa.gov.au](mailto:michael.baigent@sa.gov.au) |

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| Name: Dr Michael Nance | | | | |
| Institutional affiliation: Flinders University of South Australia | | | | |
| What is the position of this person on the research project? Recruiting psychiatrist | | | | |
| Dr Nance is the Clinical Director of Mental Health Services, SALHN.  Does this person have a current Good Clinical Practice certificate? ☒ Yes / ☐ No | | | | |
| Department and department address: Margaret Tobin Centre, College of Medicine and Public Health, Flinders Medical Centre, Bedford, Park, SA 5042 | | | | |
| Contact details: a Health address must be used | or | FUSA | email | Phone: +61 8 7117 5214  Email: [michael.nance@sa.gov.au](mailto:michael.nance@sa.gov.au) |

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| Name: Dr Lynette Rose | | | | |
| Institutional affiliation: Flinders University of South Australia | | | | |
| What is the position of this person on the research project? Recruiting psychiatrist | | | | |
| Dr Rose, head of Psychosis Unit, Marion, SALHN.  Does this person have a current Good Clinical Practice certificate? ☒ Yes / ☐ No | | | | |
| Department and department address: GP Plus Marion, 10 Milham St, Oaklands Park 5046, South Australia | | | | |
| Contact details: a Health address must be used | or | FUSA | email | Phone: +61 8 7425 8500  Email: [lynette.rose@sa.gov.au](mailto:lynette.rose@sa.gov.au) |

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| Name: Dr Titus Mohan |
| Institutional affiliation: Flinders University of South Australia |
| What is the position of this person on the research project? Recruiting psychiatrist |
| Dr Mohan is a clinical psychiatrist specialising in major depression and schizophrenia spectrum disorders.  Does this person have a current Good Clinical Practice certificate? ☒ Yes / ☐ No |

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| Department and department address: Margaret Tobin Centre, College of Medicine and Public Health, Flinders Medical Centre, Bedford, Park, SA 5042 | | | | |
| Contact details: a Health address must be used | or | FUSA | email | Phone: +61 8 8404 2570  Email: [titus.mohan@sa.gov.au](mailto:titus.mohan@sa.gov.au) |

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| Name: Associate Professor Rohan Dhillon | | | | |
| Institutional affiliation: Flinders University of South Australia | | | | |
| What is the position of this person on the research project? Recruiting psychiatrist | | | | |
| A/Prof Dhillon, Head of Acute Mental Health has extensive clinical experience with antipsychotic medications and treatment resistance.  Does this person have a current Good Clinical Practice certificate? ☒ Yes / ☐ No | | | | |
| Department and department address: College of Medicine and Public Health, Flinders Medical Centre, Bedford, Park, SA 5042 | | | | |
| Contact details: a Health address must be used | or | FUSA | email | Phone: +61 8 8404 2570  Email: [Rohan.Dhillon@sa.gov.au](mailto:Rohan.Dhillon@sa.gov.au) |

# Resources

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| What resources are necessary for the project to be conducted? |
| Please declare what funding support and amount is being sought or has been secured for this project**:** Funding is being sought from the Medical Research Future Fund - PPHR Initiative - 2020 Efficient Use of Existing Medicines. ~$1.4 million has been requested. Funding has been awarded/received from the Flinders College of Medicine and Public Health of $20,000 from the Clinical Trials uplift scheme to conduct a phase 1 pilot study of 24 participants. A research officer is in place and the pilot will be conducted once ethics approval has been obtained. |

**Project design**

Please refer to the National Statement Chapter 3.1 Elements of Research for guidance on to how to ensure this research is conducted in line with core ethical principles.

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| **Introduction** – A phase 2 pragmatic randomised clinical trial will test whether the Precision Medicine Pathway (PMP) of pharmacogenetic testing for people with treatment resistant depression and psychosis in a public mental health service. The aim is to increase remission rates, save lives, improve quality of life and save money. A phase 1 pilot project with 24 patients/participants will be conducted to establish the processes for identification, consent, recruitment of patients/participants, and trial processes including saliva collection, baseline assessments, genetic testing and preparing and providing the reports and recommendations to the psychiatrist and participants. |
| **Background and literature review –**  This research program will advance pharmacogenetic testing in Australia. The central gene, CYP2D6 that determines efficacy of many pharmaceuticals is particularly important in mental health. CYP2D6 cannot be accurately genotyped by DNA microarrays, the most common |

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| commercial method of genetic testing in Australia and worldwide. Furthermore, microarrays do not include all allelic variants and are known to assign incorrect CYP2D6 genotypes. Thus, misleading advice to clinicians based on incorrect CYP2D6 genotyping is likely to be widespread. Another technique, 2nd generation short-read sequencing, has a major challenge to assemble the many homologous tiled sequences. These two techniques lead to significant errors in the information provided. Third-generation sequencing known as long-read sequencing (LRS) is required to correctly genotype CYP2D6 by generating sequences known as phasing, not possible by microarray technologies. A study found 20% of samples re- genotyped by LRS reported a different allele type due to missed variants. Dr Lewis’ laboratory has established sample preparation, an LRS facility partner and bioinformatics to correctly phase genotypes. We will use this state-of-the-art technology in an Australian first pharmacogenetic testing for patients with psychiatric conditions. |
| **Hypothesis** - What is the scientifically valid research question being asked?   1. Does pharmacogenetic testing (PGx) in a Precision Medicine Pathway (PMP) improve the health outcomes of patients with treatment resistant depression and psychosis? 2. Is PGx cost effective for people with mental illness? 3. What factors determine how a PMP can be successfully implemented in a mental health service? |
| **Aims** - What do the investigators intend to achieve with this research project?   1. Conduct a pragmatic randomised controlled trial over 36 months of PGx using the PMP for patients with treatment resistant depression and psychosis randomised to receive either genetically informed prescribing recommendations or evidence-based guideline informed recommendations. 2. Evaluate the cost effectiveness of PGx in people with mental illness. 3. Evaluate the implementation and process outcomes of the PMP to determine barriers and promotors that could be acted upon to sustain the program and enable it to be scaled to a national level. |
| **Objectives** – Recruitment of 1032 patients for genotyping from mental health services. Trial effect size calculations require approximately 200 of these participants to have prescription intervention based on genetic testing. Patients will be followed for 18 months to determine the outcomes of both control and intervention groups. Statistical analysis will determine outcomes based on covariates including health, economic, genotype, gender and intervention status. |
| **Expected outcomes** - What do the investigators anticipate the outcomes of this research will be? The main outcome of this study will be a sustainable PMP to select patients with mental illnesses for pharmacogenetic-informed prescribing that will improve health outcomes and reduce costs. |
| **Rationale / justification** - How the research will fill any gaps and/or contribute to the field of research or contribute to existing or improved practice?  Our proposal aims to address a number of shortcomings in previous research: ***cohort***: treatment resistant people with major depression and psychosis – the most severely disabled (lost life years), at risk of suicide, most likely to benefit, highest rate of hospitalisation (therefore potential cost savings), ***setting***: public mental health services - least likely to access self- funded genetic testing and by definition are treatment resistant, ***timeframe***: each person will be followed for 18 months – previous research is short term 1-3 months so it is unknown if any benefits are sustained, ***primary outcome measure***: as an important secondary outcome, time |

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| to medication change is of interest, however, the clinical outcome of remission and reduced hospitalisation are of prime importance to patients, clinicians and funders, ***genetic testing***: use state of the art technology to provide improved accuracy of PGx than is currently available in Australia, ***implementation framework***: conduct process evaluation in parallel with a clinical trial to determine which patient groups benefit and system processes are required to implement the PMP and why. |
| **Literature review** - please explain to the committee how the literature review demonstrates the originality and relevance of your research.  It has been known for some time that highly prevalent genetic variations determine the efficacy of medicines particularly antidepressants and antipsychotics. In 2018 the Australian Medical Colleges through a position paper recommended that, pharmacogenetic-informed prescribing for psychiatric patients be implemented in routine practice based on Clinical Pharmacogenetics Implementation Consortium. More recently, in 2019 the Australian Government through the Medical Research Future Fund made a targeted call titled “Mental Health Pharmacogenomics”. This study will contribute to implementing and translating the existing well characterised pharmacological and genetic knowledge into clinical practice. |
| **Research project setting -** Research will be conducted in the mental health departments at Flinders Medical Centre, Margaret Tobin Centre, GP Plus Marion, and Noarlunga Hospital and Noarlunga Community Mental Health service. |
| **Methodological approach -** clearly describe the specific procedures or techniques that will be used to answer the research question and meet the aims.  Once enrolled, patients will receive a Mini International Neuropsychiatric Interview (MINI), which gives DSM diagnoses including mood, and psychosis diagnoses. Demographic and questionnaires along with a detailed medication record obtained from the case notes, the patient and AI2 Medicare prescription data will be obtained. At baseline, 6, 12 and 18 months all patients will be asked to complete outcome measures either face to face or by phone.  **Treatment recommendation timeline**. We plan to provide PGx to 1032 individuals over 15 months in 22 batches (N=48 per batch) for DNA collection. Genotyping and treatment recommendations for each batch will be performed within a 4-week window. With each accrual window lasting two weeks, we are able to provide treatment recommendations within 6-8 weeks of collection.  **Genotyping CYP2D6 using Long-Read Sequencing (LRS).** Using DNA samples, CYP2D6 will sequenced using Pacific Bioscience (PacBio®) third-generation technology by through the South Australian Genomics Centre in partnership with the Australian Genomics Research Facility Ltd (AGRF). AGRF is a clinically certified sequencing facility. The defining variant calls of CYP2D6 will be used to assign genotypes defined by the international Pharmacogene Variation Consortium (PharmVar). Metabolic phenotypes and clinical guidelines reported will be those defined by the international Clinical Pharmacogenetics Implementation Consortium (CPIC®).  **Genotyping CYP2C19**. The most cost-effective method to genotype CYP2C19 is by High Resolution Melting analysis will be performed at the Gavan Institute. Genotypes and phenotypes will be determined under PharmVar and (CPIC®) guidelines and reported to the clinical pharmacologist and psychiatrist.  **Global Screening Assay**. All patients will have their DNA further analysed using Illumina’s Global Screening Array-24 for confirmation of platform overlapping results. AGRF provides this service which allows further genomic validation for uncertain pharmacology reviews. |

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| **Precision Pharmacogenetic-Informed Prescribing**. Patient DNA will be haplotyped for CYP2D6 and CYP2C19 enzyme activities and assigned a phenotype for each gene from poor to ultra-rapid metabolisers. The combined CYP2D6 and CYP2C19 phenotypes and interacting medications will be reviewed by clinical pharmacologist Prof Sorich together with the prescribing clinician. Prof Roughead will oversee the monitoring and management of side effects and adverse events in relation to changes in prescriptions by the intervention group. |
| **Consumer and Community engagement –** investigators are encouraged to consult with Consumer and Community groups with the design of their research. Please outline any consultation that has occurred.  Consumers and carers are represented by Ms Carmen Hofhuis Co-Chair of the Southern Adelaide Local Health Network (SALHN) Mental Health consumer and carer advisory group, and chair of the Marion Lived Experience Group and Mr Peter King Co-Chair of the SALHN Partnering with Consumers Advisory Group. These individuals have been explicit about their own or a loved one’s experience of multiple trials of medications, distressing side effects and poor compliance. They enthusiastically support this non-invasive trial. Both consumer and carer representatives will be invited to sit on the trial advisory committee. The Marion committee have contributed to the trial design including recruitment and questions for qualitative interviews. SALHN consumers and carers will be consulted with regarding strengths and weaknesses of the PMP and improvements for wider dissemination across Australia. CI Musker has chaired mental health consumer groups at the South Australian Health & Medical Research Institute over the last 7 years and is a member of SAHMRI’s Consumer Advisory Group. We will work closely with consumers throughout this project. |
| **What are your outcome measures?**  **Aim 1:** At baseline, 6, 12 and 18 months all patients will be asked to complete outcome measures either face to face or by phone. Demographic measures: include age, gender, ethnicity, marital, education, employment status, living situation. Primary outcomes: Remission as determined by a cut off <10 on the PHQ9 and the 8 items of the PANSS each item should be ≤3 for a period of 6 months. Secondary outcomes: Readmission rates as indicated by ED and hospital in-patient admissions, Patient Health Questionnaire (PHQ-9) to measure depression, the PANSS to measure psychosis, the Liverpool University Neuroleptic Side Effects Scale (LUNSERS) and the EQ-5D to measure quality of life. Prescribed medications will be monitored by the AI2 software CIG Musker will oversee patient assessments and maximise completion of follow-ups.  **Aim 2:** Economic evaluation will be conducted to assess the cost-effectiveness of pharmacogenetic-informed clinical management compared to usual care (CIH Afzali).  **Aim 3: Implementation data includes** t  he number of patients approached, enrolled into the program, genetic tests provided, psychiatrists and medical officers involved, revised prescribing recommendations made, and recommendations implemented. We will purposefully select and use a semi-structured interview with 10 intervention patients varied in gender, age, age at diagnosis and living situation, 3 carers and 10 project and health staff to identify inhibitors and promotors within the health system, affecting uptake of genetic testing and of the prescribing recommendations.  Datasets will be compared and contrasted to triangulate perspectives of all participant groups. Integration of quantitative and qualitative findings will compare and contrast PMP evaluation outcomes. |
| **Project duration:**  Three years. |

# Participant selection and activities

Explain how participants will be recruited or how their data will be selected (e.g. for a registry).

Describe sources and methods that will be employed in the identification and recruitment/selection of potential participants (e.g., clinics, referring doctors, adverts, and time periods) or of historical data (e.g. medical records, databases).

You should make a distinction between how you will recruit/select control participants compared to other groups if performing a comparative intervention.

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| **How many participants will be selected for the study?** 1032 |
| **How are they identified as possible participants?** Patients with two or more unsuccessful treatments of antidepressant and or antipsychotic medications will be invited to participate in the trial. Unsuccessful treatments include lack of symptom relief and lack of adherence to medication due to side-effects.  **Pre-screen for eligibility – waiver of consent**  The recruitment method must be compliant with the Health Care Act 2008. If you need to access a patient’s medical records to pre-screen for eligible participants, and you do not have prior patient consent to do so or are not part of the patient’s clinical care team, you will need to apply for an exemption under 93(3)(f).  Are you requesting a waiver of consent to pre-screen?  ☒ No – I am part of the patient’s clinical care team.  □ Yes  Under s93(3),(f) of the Health Care Act 2008, we wish to apply for an exemption of patient consent to access their personal information for research purposes. In order to identify suitable participants for this research project, <specify who or a title i.e. study coordinator> will be required to access <specify what is being accessed>, prior to obtaining consent from the patient.  **How will participants be recruited into the study**? Please provide a detailed step by step description of the recruitment methods. Clinical psychiatrists will invite participants by providing an information sheet to their treatment resistant patients identified from all current and consecutive inpatients and outpatients. As possible participants are either in-patients or out-patients, advertising will not be required. Patients will not respond to their psychiatrist; they may join the study using the research teams contact details on the information.  **How will they be approached?** Initially their psychiatrist will provide the participant invitation, if the patient wishes to join the study, they will contact the research team members or by being approached by the research assistant whose details of potentially eligible participants are provided by the treating psychiatrist. The research team including mental health nurses will obtain consent, saliva samples and psychiatric questionnaires. |

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| **What are the inclusion and exclusion criteria? -** Detail the characteristics that clearly describe the study population that are required to be either included or excluded in the research.  **Inclusion:** Adults 18-65 years, with a diagnosis of treatment resistant MDD or SSD (schizophrenia, schizoaffective disorder, bipolar disorder), both with or without comorbid disorders confirmed by the Mini International Neuropsychiatric Interview (MINI) and are taking prescribed medications. Treatment resistance is defined as have trialed 2 or more medications with inadequate treatment response for a minimum of 4 months as determined by the patient and psychiatrist  **Exclusion:** Intellectual or cognitive or language difficulty that prohibits an understanding or participation in the program, active psychosis, severe distress or suicidality, or substance intoxication. |
| **Participant commitment** -What will their participation involve? I.e. study visits, procedures, tests, tissue samples, questionnaires, wearing of any devices.  Participants will submit a saliva sample using a standard collection kit. They will undergo assessment at baseline, including the Mini International Neuropsychiatric Interview (MINI) which gives DSM diagnoses including mood, and psychosis diagnoses. Demographic and questionnaires along with a detailed medication record obtained from the case notes, the patient and AI2 Medicare prescription data will be obtained. 6, 12 and 18 months using the Patient Health Questionnaire (PHQ-9) to measure depression, the PANSS to measure psychosis, the Liverpool University Neuroleptic Side Effects Scale (LUNSERS) and the EQ-5D to measure quality of life. The baseline assessment, saliva collection and questionnaires will take 40-60 minutes. The research assistant who will conduct the recruitment and consenting process and on the same day will also take a saliva sample and undertake baseline assessments and questionnaires. The saliva samples will be stored in a refrigerator at the Margaret Tobin Centre and sent as a batch twice weekly to CI Lewis at SAHMRI for coding and processing for transfer to the testing sites SAGC and QUT. When the genotyping results are returned within 2-4 weeks to CI Lewis at SHMRI, the Flinders clinical trials centre will be contacted to provide the randomisation allocation as per the randomisation protocol.  Qualitative evaluation: For Aim 3 we will purposefully select and use a semi-structured interview with 10 intervention patients varied in gender, age, age at diagnosis and living situation. In addition, we will seek expressions of interest via email to carers and research staff and staff with intervention participants to randomly select 3 carers and 10 project and health staff to identify inhibitors and promotors, affecting uptake of genetic testing and the prescribing recommendations and to avoid any perceived coercion to participate in the research. |
| **Participant follow up** – how are participants monitored during the study? Patients will be followed up at 6, 12 and 18-months to complete mood questionnaires taking between 15-30 minutes. Any hospital admissions or clinical visits will also be noted. These data collection sessions will occur before or after usual clinic visits which occur at a minimum of 3 monthly and often sooner depending on clinical need. No extra visits or attendances are required hence no additional expenses will be required to reimburse participants. |

## Consent

Please refer to the National Statement 2.2 for guidance on consenting participants.

Where possible, informed consent should be sought from individuals to participate in research or to access their data for research purposes.

Consent can provided in writing, implied (i.e. by return of a survey), opt in, opt out or verbally.

If consent cannot be obtained from the participant, a waiver of consent can be applied for which is reviewed and approved by the SAC HREC. The waiver of consent must be justified using the National Statement chapter 2.3.9 and 2.3.10 (a) to (i) in the HREA.

The investigator(s) should: · Determine, according to level of risk to participants, who of the study team is appropriate to lead the participant informed consent process. This should be documented on the “Delegation of Duties” log. (ICH GCP 5.7)

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| **How you will be obtaining consent and/or what alternatives you will be using**: Consent may be obtained on a printed sheet or by email. |

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| **Are you requesting a waiver of consent**  **□ Yes –** please justify why the waiver of consent is appropriate in the HREA  **☒ No** |
| **Which investigators will issue the information sheets and consent forms**: Any of the clinical staff or clinical research team may issue information and consent forms. |
| **How much time will participants have to consider participation**:  Participants may take several weeks to consider participating. After this time one of the research team may contact them to enquire if they are still considering their invitation. |
| **Please specify which investigators will obtain consent from participants**: Consents will be  All of the clinical staff will be able to obtain consent in person, and any of the research team when participants choose to consent electronically. |
| **Will there be an opportunity to confirm or renegotiate consent during the research project**? – I.e. the capacity of the participant changes or the terms of consent / participation changes. Consent can be renegotiated although participation only includes a single saliva sample and questionnaires. Health outcomes without questionnaire data will still contribute to the study. |
| **Who will be confirming or renegotiating consent with participants and what process will be undertaken?** As the study demands on participants are not complicated negotiation will not be difficult. The participant can stay in the study in a limited capacity by not completing the follow up visits. However, the participant genotypes will contribute to the study. |
| **Conflicts of interest:** Please refer to the National Statement chapter 5.4, and your institutional policy for guidance.  □ Yes / ☒ No  **Please provide details of the conflict of interest: How will the conflict be managed?** |

# Ethical considerations

**Please describe the risk and burden associated with your research**. The National Statement chapter 2.1 provides guidance and advice on the definition of risk and how to gauge and manage it.

It is expected most participants will have either a managed diagnosis for depression and or psychosis. In the clinical mental health settings these risks are continually managed, and no unforeseen risks are expected. Mental health services currently manage attempted and completed suicides and through

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| pharmacogenomic intervention expect these to be reduced. |
| **How will any risks be managed?**  Adverse effects will be monitored and evaluated by a sub-committee that encompasses pharmagenomic guided prescription interventions. When researchers engage with participants, appropriate hygiene will be practiced. Saliva collection tubes will be kept in a sealed bag and processed in a biological safety cabinet. Surfaces in the clinical rooms will be wiped with disinfectant following participant visits. |
| **Benefits** – please identify and explain the expected outcomes and benefits of the study  Participants will benefit by obtaining their phenotypes for drug metabolism that are directly relevant to their treatment. The team will provide time to explain the value and use of their results. Clinicians are better able to treat people that know their genotype especially for treatment resistant patients who are fast or slow metabolisers. Information will include clear clinical support guidelines for participants and their health practitioners. |
| **Does a dependent or unequal relationship exist between the participant and the researcher?**  Please refer to the National Statement 4.3 for advice and guidance on how to manage this**.**  **□** Yes -  How will the dependent / unequal relationship be managed? Click here to enter text.  **☒** No |

## Data management – as required in addition to that outlined in your HREA

As per the National Statement 3.1.45, researchers must have a data management plan in place.

The Office for Research would like to remind researchers that the disposal of research records must be made in accordance with The State Records Act 1997 (the Act). Under that Act records must be disposed of as outlined in the general disposal schedules.

**Public health institutions** fall under general disposal schedule 28. As per item 6 of general disposal schedule 28, the researchers records of research including results, notes, completed questionnaires, signed consent forms, data, reports, and study findings must be kept for 15 years after the research project has been completed before being destroyed. This includes all types of research.

**Universities** fall under general disposal schedule 24. As per section 9 of general disposal schedule 24 research data records should be kept for a duration according to the nature of the study. For short term research projects such as study research projects, data should be kept for 1 year after last action. Research data from clinical trials should be kept for 15 years after action completed. All other research data and results should be kept for 5 years after publication, conclusion, or abandonment of the project. Data should be destroyed after the mandatory retention period.

Unless informed consent has been obtained from the participant, or legally authorised person, or the HREC has expressly approved otherwise, personal information used or disclosed for research purposes, must be de-identified. Only SA Health employees will perform the de-identification process prior to releasing the information for research purposes.

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| **Who will collect the study data / information?** Only SA Health employees can access patient data for research purposes. Students and non-SA Health employees cannot access patient records for research purposes under any circumstances. Only those authorised to access patient data will do so. The research team will conduct questionnaires that are independent of existing clinical patient data. |
| **What format will the data or information be stored?**  All questionnaire and genetic data will retain an assigned randomised code. The key to sample codes will be kept encrypted and stored securely. |
| **Please provide details regarding training of the research team on maintaining the integrity and security of the data**  The trial project manager will establish data collection and management system using Qualtrics. They will use Qualtrics to monitor the integrity of data collection by the research officers and provide updates to the trial project committee weekly then fortnightly over the life of the trial. The trial project manager will be responsible for data collection problem solving with clinicians and project staff to correct any short falls. |
| **What conditions can the data be accessed or granted to others?** Only unidentifiable summary data will be shared with the research team and presented in any reports or publications. Access to raw data will not be granted to those outside of the research team. |
| **How will the research data be stored and what security measures are in place to protect it?**  All data analysis will be performed on data only identified by a code. This is standard practice to remove any unconscious bias and protect individuals. Our analysis of DNA sequence accuracy does not require an individual’s identity be known. |
| **How will you provide access to, disclose, use/re-use or transfer the data?**  All data will be unidentifiable. Only secure access will be used to share or transfer data. Only summary and not raw genetic data will be retained for the duration of the study. |
| **How long will the data be retained for?**  □ The data will be kept for 15 years – for all SA Health research  ☒ The data will be kept for 5 years – for all University research, |
| **What plans are in place to store / archive the study data once the research is completed?** Unidentifiable data with consent will be stored securely on allocated servers. |
| **How will the study data be destroyed?**  When digital data is deleted it will be securely deleted to prevent recovery. |

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| **Matching and sampling strategies:**  A randomised non-sequential code for all participants will be securely kept separate to all de-identified data and saliva samples. Randomisation of participants will be balanced for sex and age between the control and intervention groups. |
| **Accounting for potential bias, confounding factors and missing information:**  Randomisation will be determined prior to participants joining the study and will not be a clinical decision as to which arm of the trial.. After informed consent, eligible patients will receive Pharmacogenomic (PGx) testing. Saliva samples stored in a refrigerator at Flinders Medical Centre (FMC) will be transferred twice weekly to CI Lewis at SAHMRI where it will be coded and deidentified for transfer to the testing facilities at QUT and South Australian Genomics Centre at SAHMRI. Once the result is known (2-4 weeks) the participant will be randomised to a study group (see below). Using a predictive enrichment design, to provide sufficient numbers of extreme metabolisers (EMs) in each group from which to demonstrate an effect of PGx, the proportion of EMs in each group will be doubled from 10% to 20%. EMs will be randomly allocated to 1 of 2 study arms, whereas normal metabolisers (NMs) will be randomized to 1 of 2 study arms or to exclusion in a 1:1:3 sequence. Randomisation will be blocked to increase the likelihood of scheduled group sizes, using a standard permutated block algorithm in which block sizes will be randomly chosen to protect concealment. Block randomisation within strata will be used to ensure equal proportions of Major Depressive Disorder (MDD) and Schizophrenia Spectrum Disorders (SSD). A bio-statistician will independently generate random sequences for each stratum using Stata 16.1 software (StataCorp, 2019) and deliver these to the Flinders Clinical Trials Centre. Once a genetic test result is received by CI Lewis, research staff will contact the Flinders Clinical Trials Centre to obtain the trial group allocation then notify the participant. Staff enrolling patients, as well as those collecting and entering data and administering interventions, will not know in advance which treatment group the next patient will receive. As each genetic result and recommendations is provided to the psychiatrist to discuss with their patient, the patient will not be blinded to whether their treating clinician will know their genotype results. Similarly, in the control group, the psychiatrist will receive the clinical guideline based recommendations which means that neither the patient nor the psychiatrist will be aware of the genotype results. |
| **Sample size and statistical or power issues –** Make sure the size and profile of the sample to be recruited is adequate to answer the research question – please provide details**:**  As above, EMs will be randomly allocated to 1 of 2 study arms, whereas normal metabolisers (NMs) will be randomized to 1 of 2 study arms or to exclusion in a 1:1:3 sequence. To compute the required sample size for primary outcome of remission at 12 months confirmed by the Mini International Neuropsychiatric Interview, we specify the values  0.10 and 0.35 as the control and PMP-group proportions. Based on a binomial two-tailed test, type I error rate of 5% and power of 80%, we calculate the number of EMs needed in each arm to be 43. Assuming a prevalence of 10% of EMs, both study groups will aim to include 43 EMs and 155 NMs, while a total of 465 NMs will be randomly excluded to elevate the proportion of EMs from 10% to 22%. To account for 20% attrition we will need to recruit a total sample of 1032 patients. Missing information will be treated using established statistical protocols. |
| **How will you measure, manipulate and/or analyse the information collected?** The gene sequences will be bioinformatically analysed for functional variants. The bioinformatic technique of note is haplotype phasing to determine which variants are grouped on the maternally and paternally inherited genes. The health outcomes, costs and questionnaire will be modelled by the statistician and health economist. |
| **Data linkage –** Our intention is to access patient Medicare data and use a digital mental health platform created by A/Prof. Bidargaddi, called AI-squared. These data will provide prescription adherence and hospitalisation rates which are associated with poor health outcomes. |
| **What impact will a participant withdrawing have on the data and how will this be responded to?** The number of patients, 1032 has been calculated to accommodate participant withdrawals while maintaining the study effect size. If a participant wishes to withdraw for any reason, they are free to do so. |

# Results, reporting, outcomes and future plans

## Post approval monitoring and reporting

Once you have received ethics and governance authorisation for your research project, there are mandatory reporting requirements you must adhere to as per The National Statement chapter 5.5.

* Annual review – this is required annually for the life of the audit, on the anniversary of the approval date. Please use the template on our website.
* Final report – this is required to be submitted on completion of the audit. Please use the template on our website

Please refer to the Office for Research Reporting and Monitoring guidelines on our website for the mandatory reporting requirements for this research project.

Failure to submit the required reports of a breach of the NHRMC Australian Code for the Responsible Conduct of Research R17, R22, the National Statement chapter 5.5 and the terms and conditions of the ethical approval of the study. Failure to submit the required report may result in the ethics approval being withdrawn and the application closed.

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| **Please detail your plans for the return of the research results to the participants**: Research participants will be provided with their results in the form of a practical guide in the presence of their psychiatrist. For the pilot all 24 participants will be receiving their results with their psychiatrist.  There is no control or excluded group.  In the full phase 2 RCT study, those with normal metabolism that are excluded will be provided with their test results in the presence of their psychiatrist/doctor within 2 months of their randomisation being known. The control participants will receive their results and recommendations within 2 months of the completion of their 18 month follow up period. |
| **What are your plans for dissemination and publication of project outcomes**: The results will be published in internationally peer reviewed journals. No participant will be identifiable in any publications. |
| **Please detail other potential uses of the data at the end of the project**: The health and economic data will be used to determine the value of pharmacogenomic intervention for mental health services. |
| **What are your plans for sharing and/or future use of data and/or follow-up research?** i.e. anticipated secondary use of data: All data and samples will be de-identified. Future studies may be combined with this study in increase the statistical power of pharmacogenetic intervention for depression and psychosis. |

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| **What is the project closure process?** When all study participants in both the control and intervention groups have been followed up to assess their health outcomes, and statistical and economic analyses are performed on data collected. Final reports and publications will then be prepared, including a final report to the HREC. De-identified data and saliva samples will be stored on a secure server and in secure biobanks respectively. After five years all bio-specimens will be destroyed and discarded. |