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Protocol for a Young Adult Mental Health (Uspace) Cohort: Personalising multidimensional care in young people admitted to hospital.

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ABSTRACT

Introduction To deliver mental health care that meets the unique needs of young people, new multidimensional, measurement-based and highly personalised health service care models are needed. Currently, the literature on personalised and measurement-based mental health care is inadequate with major gaps in the development and evaluation of 21St Century service models. As clinical presentations of mental ill health in young people are very heterogeneous, and clinical and functional outcomes are often sub-optimal, providing treatment in a more person-centered and responsive fashion is critical to improving individual outcomes. More personalised care also requires concurrent assessment of factors relating to broad outcomes and underlying neurobiology. This study builds on a completed feasibility study and will be the first to incorporate clinical, cognitive, circadian, metabolic and hormonal profiling with personalised and measurement-baed care in a cohort of young people admitted to hospital.

Methods and analysis This prospective, transdiagnostic, observational study will be offered to all young people between the ages of 16 and 30 years admitted to the inpatient unit of the participating centre. In total, 400 participants will be recruited to the "Personalised Multidimensional Care" study . On admission to hospital young people will undergo clinical and diagnostic assessment, cognitive testing, self-report questionnaires, metabolic and hormonal data collection, and anthropomorphic measurements. Participants will wear an actigraphy watch for at least one week during admission to measure circadian patterns and sleep-wake cycles. A feedback session between clinician and participant will occur after clinical and other laboratory assessments and before discharge to tailor individual treatment plans, explain the ongoing process of measurement-based care and provide participant and family education. Time-series relationships between clincal, laboratory and other objective measurements will be analysed using appropriate multivariate statistical methods.

Ethics and dissemination This study protocol was approved by the Human Research Ethics Committees of the University of Sydney (HREC USYD 2015/867) and St Vincent's Hospital (HREC SVH 17/045). This study will be published upon completion in a peer-reviewed journal.

ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS OF THIS STUDY:

- This study will follow a large cohort (n=400) of young people admitted to hospital for mental health care to examine determinants of clinically significant mental and physical health, and social, educational and occupational outcomes.
- As an observational study this will be naturalistic in fashion and no randomisation or control group will be included.
- The multifaceted variables collected such as anthropomorphic, metabolic, hormonal, cognitive, circadian and symptomatic data will offer information on the multifactorial variables leading to mental and physical ill health and treatment outcomes.
- Heterogeneity of the clinical presentations to an inpatient setting strengthens the study's generalisability to other similarly severe presentations of mental ill-health in young people.

KEYWORDS: Study protocol, observational study, affective disorder, young adult, mood and psychotic disorders, measurement based care, personalised care

INTRODUCTION

Clinical presentations of mental ill-health in young people are very heterogeneous in fashion. Current diagnostic criteria often fit poorly with the subthreshold or mixed presentations that are common in young people [1]. Typically, mental health care has relied on these diagnostic criteria to inform clinical decisions, leading to stereotyped and limited treatment responses which are often not well matched to individual needs. In accordance with a shift in health-care services and research priorities from evidence-based to personalised medicine [2], personalised, sequenced, multidisciplinary and more measurement-based interventions are new goals. These aim to translate evidence-based methodologies into individual treatment plans [2, 3]. Consequently, we have proposed a highly personalised and measurement-based care model for use in youth mental health services [4]. This transdiagnostic, person-centered model of care emphasises early access to personalised care through a comprehensive multidimensional assessment of various clinical and functional domains [5], including social and occupational functioning, self-harm and suicide risk, alcohol and substance misuse, physical health, clinical severity and stage (Stage 1a (non-specific symptoms) to Stage 4 (severe, persistent, and unremitting illness)) [6, 7], and illness subtypes (psychosis, anxious depression, bipolar spectrum). It also links with putative pathophysiological pathways (neurodevelopmental, hyperarousal, circadian) as well as individual illness trajectories [1, 8-10]. Such a clinical stage-appropriate and transdiagnostic framework may lead to improved clinical outcomes as it helps to guide the selection of treatments based on individual needs and symptom burden as well as underlying pathophysiological mechanisms [1].

Objectives of the Study and Conceptual Framework

The "Personalised Multidimensional Care" study is generating multidimensional – i.e. clinical, functional, cognitive, circadian, metabolic, and hormonal – profiles for participants with clinician feedback, specifically addressing individual issues affecting participant outcomes such as cognitive impairments, disturbed sleep-wake behaviours and circadian rhythms, clinical symptoms, and functional impairments. Cognitive testing and circadian profiling is not yet often routinely available in standard clinical care but is very important in understanding the relationship between symptoms and functioning, as neuropsychological deficits and dysregulated sleep-wake cycles have been linked to poorer functional outcomes [8, 11-14]. Furthermore, incorporation of metabolic and hormonal profiles is imperative in capturing, evaluating and treating co-morbid and contributing conditions such as metabolic syndrome and

polycystic ovarian syndrome (PCOS) which are often found concurrently in young psychiatric patients [15-18].

The "Personalised Multidimensional Care" study focuses on an inpatient young adult mental health clinic (Uspace). A key strength of this cohort is in its heterogeneity and ability to capture a presently severe hospitalised sample of young adults with varying mental disorders. The cohort will allow for studying a wide range of personalised interventions, whilst also examining the longitudinal trajectory of this young, more severely ill cohort, and the associations between detailed clinical, hormonal and metabolic profiles, social, neurocognitive, functional and circadian outcomes.

As previously demonstrated, the use of Health Information Technologies (HITs) (computerised, self-reported e-health technologies such as the InnoWell Platform (Project Synergy, InnoWell Pty Ltd) [19]) facilitates systematic multidimensional assessment in young people seeking help [20], enables opportune and timely responses from service providers and clinicians [20], and will, therefore, facilitate the development and delivery of highly personalised and measurement-based treatment plans.

The multidimensional assessments (clinical, functional, cognitive, circadian, metabolic, and hormonal) and resulting personalised interventions will enhance knowledge and inform clinical practice to improve standard clinical care in an inpatient unit. However, personalised care means implementation of new protocols, training, and practice, as well as cultivating a new conceptual framework [21, 22]. This study will integrate these approaches to help further knowledge in the field and facilitate translational changes to mental health care. Importantly, the personalised care approach based on multidimensional assessments is a collaborative approach and requires multidisciplinary teams of health professionals and involves shared decision-making based on the participant's best interests [22, 23].

METHODS AND ANALYSIS

Study design and setting

This prospective, transdiagnostic, observational study will offer recruitment to all inpatients aged 16-30 admitted to the Young Adult Mental Health Unit (Uspace), St Vincent's Private Hospital Sydney, Australia. Uspace is a voluntary private mental health service, targeted to the needs of young adults. Furthermore, it is a unique multidisciplinary clinical setting for research.

Patients are referred for the assessment of mental health problems; with a mission to promote recovery and psychological well-being of young adults with severe and emerging mental health problems.

This "Personalised Multidimensional Care" study will be conducted over a period of 5 years, from early 2020, with assessments at baseline and possible longitudinal follow-up available upon participant consent up to 24 months. The selection of participants as well as the assessments are consistent with the transdiagnostic 'Research Domain Criteria' (RDoC) approach [24] as a means of classifying mental disorders based on neurobiological and behavioural (in this case, functional, circadian, hormonal, metabolic, and cognitive) measures. Furthermore, this study utilizes a subject sample (i.e. across the inpatient unit) with the appropriate variance as advocated by proponents of the RDoC approach [25].

Participant and public involvement

The Health Information Technology (HIT) system (InnoWell Platform (InnoWell Pty Ltd) [19] which will be used for collection of self-report data in the study has been developed with participant and public involvement. This study also involves feedback about cognitive and circadian profiles, providing individually tailored information regarding their strengths and weaknesses. Furthermore, the results of this study will be disseminated to the participants upon conclusion.

Patient Cohort

Study participants are currently admitted young adult inpatients, aged 16-30, presenting with a severe affective episode (i.e. depressive, manic, anxious; including those with psychotic features).

Exclusion criteria for this study are: (i) insufficient fluency in the English language to participate in the cognitive testing; (ii) inability to consent due to intellectual impairment (for example, IQ < 70 as determined by the treating psychiatrist/psychologist) or severity of mental illness (as determined by the treating psychiatrist/psychologist); and (iii) refusal to provide informed consent.

Comorbid or pre-existing childhood-onset conditions (for example Attention Deficit Hyperactivity Disorder (ADHD) and conduct disorder), as well as alcohol or other substance misuse or autistic spectrum disorders are not exclusion criteria.

Study course and procedures

Through consecutive referral, eligible participants who are newly admitted to Uspace will be booked in to complete neurocognitive testing and self-report questionnaires after informed written consent. Participants' availability and booking schedule is based around their own routine appointments and groups as inpatients, with most participants being booked within four days of admission. Hormonal and metabolic measures are routinely collected at Uspace on admission as part of standard clinical care, this data will also be used for research purposes on and during admission as indicated by standard of care, regardless of entry into the study. Neurocognitive testing (CANTAB) is completed on a tablet devide, taking between 35 and 45 minutes. The self-report questionnaire will be completed the day after neurocognitive testing, taking approximately 45 to 60 minutes. Actigraphy watches will be set up to record and given to patients to wear once informed consent is provided. No supervision is needed during wearing of the actiwatches. The appropriate clinician that admitted the corresponding participant during the admission process will complete a 'Clinical Assessment Form'. The multidimensional assessments as well as the feedback session will inform personalised interventions offered to the young adult participants in a shared decision-making process.

Assessments

Clinical Presentation

The clinical presentation is captured in the 'Clinical Assessment Form'. Participants are determined to have a primary diagnosis of an affective disorder. These include depressive disorder, anxiety disorder, bipolar disorder, or affective psychosis through consensus diagnosis; that is, via multidisciplinary clinical assessment (by psychiatrists, psychologists and allied health professionals). In addition, this form records information regarding the participants current episode/presentation, psychiatric history, medical history, social and occupational functioning, clinical severity/improvement and clinical stage.

In addition, menstrual history and symptoms are assessed in the female population using a self-report questionnaire capturing age of menarche, regularity of the period, amenorrhoea, period pain, body hair, skin, mood, sleep and fatigue symptoms.

Self-report Questionnaire

The self-report questionnaire is implemented within HIT system (InnoWell Platform (InnoWell Pty Ltd) [19] and is, thus, electronically completed on a touchscreen device (e.g. tablet device). It captures key clinical information regarding the following:

Demographics

Biological sex is specified, and age is calculated. Current engagement in part- or full-time education or employment is recorded to determine Not in Education, Employment, or Training (NEET) status. NEET is assigned if there is no full- or part-time education, employment, training, or volunteer work. Current receipt of any government benefits is also recorded.

Personal Mental Illness History

Known childhood-onset disorders (i.e. with clear onset prior to 12 years old) are recorded in addition to current diagnoses.

Family History of Mental Illness

Known family history of mental illness in first degree relatives is recorded.

Treatment Utilisation/History

Exposure to classes of medication (antidepressant, antipsychotic, mood stabiliser, or stimulant medication), and hospitalisation overnight or longer due to a mental health problem (including specification of hospitalisation due to illness severity or suicidality) are recorded.

Alcohol and Substance Use

The presence of any reported use of tobacco, alcohol, cannabis, stimulants, or other drugs is recorded.

Clinical Symptoms

Initial questions obtain key demographic and clinical information, focusing on critical illness course variables (for example, onset of symptoms, hospitalizations, age of first help seeking). Standardised questionnaires include the 10-item Kessler Psychological Distress Scale (K-10) [26] to detect psychological distress, with scores ranging between 10 and 50 (a score over 30 representing a likely severe mental disorder); Quick Inventory of Depressive Symptomatology (QIDS-16) [27] to assess severity of depressive symptoms, with scores ranging between 1 and

27 (a higher score representing greater severity of depression); Overall Anxiety Severity and Impairment Scale (OASIS), a 5-item measure for assessment of severity and impairment in regard to anxiety symptoms [28], with scores ranging between 0 and 20 (a higher score representing a higher frequency and severity of anxiety (across anxiety disorders); Psychosis Screener derived from Community Assessment of Psychic Experiences (CAPE)[29], a positive symptoms scale and psychosis screener, developed to measure the lifetime prevalence of psychotic-like experiences in the general population; Hypomania Screener derived from the Altman Self-Rating Mania Scale (ASRM) [30], a 5-item self-rating scale to assess the severity of manic symptoms, a higher score (five or more) indicating a high probability of a manic or hypomanic condition; Suicidal Ideation Attributes Scale (SIDAS) [31], a 5-item scale to screen participants for suicidal thoughts and severity of these thoughts, with scores ranging between 0 and 50 (a higher score representing more severe suicidal thoughts (a score over 21 being in the high risk category); and, the Somatic and Psychological Health Report (SPHERE-12) [32], a 12-item measure to screen for current depression and/or anxiety-like symptoms (a score of two or more on the psychological subscale and a score of three or more on the somatic subscale indicating current depression and/or anxiety-like symptoms).

Neurocognitive Screening

Self-reported, non-structured, standardised questions in regard to the participant's own sense of cognition will be assessed prior to testing (for example, changes in everyday thinking skills and neurocognitive abilities).

A trained research psychologist or psychiatric registrar at Uspace will administer the cognitive testing battery, which includes computerized assessments. First, premorbid intellectual functioning ('predicted IQ') is estimated on the basis of performance on the Wechsler Test of Adult Reading[33]. Following this, participants complete tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB)[34] on an HIT platform. CANTAB tests have the advantage of being largely non-verbal (i.e. language-independent, culture-free) and have been described in detail elsewhere [34-36]. Five tasks are included in this study: the Motor Screening Task (MOT), an introductory task to prepare participants for testing (i.e. not included in overall results) using induction of sensorimotor and comprehension; the Verbal Recognition Memory task (VRM immediate and recall/delayed) assessing 'verbal memory and new learning' indexed by the encoding and subsequent retrieval of verbal information scores; the Attention Switching Task (AST) assessing 'mental flexibility' and indexed by the total

adjusted score; the Paired Association Learning task (PAL) assessing 'visuo-spatial learning and memory' indexed by the total adjusted errors score from; and, the Rapid Visual Processing task (RVP) assessing 'sustained attention' and indexed by the RVP A prime (sensitivity to the target).

Participants' individual, normed results are calculated by a trained research psychologist within two to three days of completion of cognitive testing battery. Calculation of CANTAB z-scores are completed for each participant. While each participant's predicted IQ is assessed in the cognitive screener, this is specifically to personalize results based on each participant's age, education and background, compared to 'demographically corrected' standardised scores (z-scores) using an internal normative database of healthy controls (http://www.camocog.com).

Sleep-Wake Cycle/Circadian Profile

Participants are given an actigraphy watch (GENEActiv watch, Activinsights Ltd., Kimbolton, UK) to wear on the non-dominant wrist during the admission period for a maximum of 14 days and a minimum of 6 days. This actigraph records motor activity levels, skin temperature, and ambient light exposure continuously at a rate of 30hz for the duration of the recording period. The GENEActiv devices have been validated against several types of accelerometry-based activity monitors[37-39] as well as for sleep-wake scoring [40]. More specifically, sleep-wake detection in data collected with the GENEActiv devices has been found to have strong reliability and validity when compared to data collected with other GENEActiv monitors or with Actiwatch Spectrum devices (a well-established instrument in sleep and circadian research) [40]. For over three decades, actigraphy monitors like the GENEActiv devices have been considered as non-invasive instruments to measure sleep and activity patterns and have been used extensively for research purposes in diverse clinical settings including: sleep disorders, various medical illnesses (e.g. cancer, HIV, traumatic brain injuries, neurodegenerative diseases) and mental disorders (e.g. anxiety, depression, bipolar and psychotic disorders).

Metabolic and hormonal profiles

As standard clinical care, metabolic data, including measures of body, weight, waist circumference, as well as blood pressure readings and routine metabolic bloods (including e.g. glucose, insulin, cholesterol, low- and high-density lipoprotein, triglycerides etc.) are routinely collected at Uspace on admission, this data will be used for research purposes. After assessment by a clinician, women with clinical evidence of co-morbid polycystic ovarian syndrome

(PCOS) will undergo further hormonal assays (including e.g. oestradiol, Dehydroepiandrosterone Sulfate, Anti Mullerian Hormone) collected as standard clinical care.

Feedback and personalised care

Once both the self-report questionnaire and cognitive testing have been completed by the participant, and the clinical assessment form has been completed by the admitting clinician, a feedback report will be generated (within 7 days of the completed assessments). A brief feedback session will be organised with the participant in order to go through and explain results and what that means in terms of more personalised intervention. This feedback report and session will be between the participant, treating clinician and clinical researcher. The feedback session will be part of the standard clinical care whereby the results of the testing will be explained in detail to the participant, management options will be explored, and any questions the participant may have will be addressed; furthermore, briefing will occur during the participant's weekly clinical reviews. The feedback session aims to give the participant a better understanding of certain aspects of their mental health and wellbeing and what they, and their clinicians, can do to improve those areas. A feedback report of the actigraphy (sleep-wake cycle and circadian) assessment results will be provided to the clinician upon completion of the total time (maximum 14 days) wearing the actigraphy watch.

The results of the multidimensional assessments – including clinical, functional, cognitive, circadian, metabolic, and hormonal profiles – as well as the feedback session will inform personalised interventions offered to the young adult participant in a shared decision-making process.

Sample size calculation

We aim to have a sample size of 400, based on the number of inpatients admitted to Uspace over this period.

Data analysis plan

Once completed, the data from the self-report assessment is collated, and displays a detailed and immediate dashboard of results. This information is available to a trained research psychologist immediately upon the participant's completion of the self-report assessment and will be used to prepare the feedback report.

This "Personalised Multidimensional Care" study allows for the assessment of multidimensional – i.e. clinical, functional, cognitive, circadian, metabolic, and hormonal – profiles for young adult participants. This includes:

1. Evaluating parameters affecting participant outcomes such as cognitive impairments, disturbed sleep-wake behaviours and circadian rhythms, clinical symptoms, and functional impairments.
2. Investigating associations between metabolic, hormonal, clinical, self-report, and circadian factors.
3. Comparisons with similar data from young people presenting to outpatient youth mental health services (e.g. Brain and Mind Centre cohorts [9, 41, 42]).

Besides the use of statistical standard methods (ANOVA, correlations, and regression analysis), high-level statistical techniques including mixed-effects/ multilevel modelling, Bayesian modelling [43-45], structural equation modelling [46], and data-driven techniques [47-49] such as hierarchical cluster analysis [12, 21, 50], latent profile analysis [51], and group-based trajectory modelling [52] will be applied.

ETHICS AND DISSEMINATION

This study protocol was approved by the University of Sydney (HREC USYD 2015/867) and St Vincent's Hospital Human Research Ethics Committees (HREC SVH 17/045). Following confirmation that potential participants from the Uspace inpatient cohort are of mental and intellectual capacity to give informed consent, and have no language barriers, a complete description of the study will be discussed and eligible participants will be given a Participant Information Sheet and Consent Form and followed-up by the researcher for informed written consent, no less than 24 hours later, with those under the age of 18 having their parent or guardian also consent. This study is minimally invasive, and any adverse outcomes will inform procedure.

All participant data will be de-identified and stored in accordance with applicable security standards; therefore, the privacy of all participants will be protected.

The research findings will be disseminated through publications in peer-reviewed journals and conference proceedings, and participant data will be non-identifiable.

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CONTRIBUTORS

IBH and EMS conceived the research idea, designed the study, and are the principal investigators (for corresponding sites); AMT contributed to study conception, wrote the study protocol with input of JSC (actigraphy), AG (hormonal and metabolic measurements), KH, LP, and EMS. AMT manages the study with input of EMS, KH, and LP. EMS contributes to clinical organization; KH and LP manage patient unit participation and supervision. AMT wrote the first draft of the manuscript; CR, AG and YJCS contributed to major edits in later versions. All authors contributed to discussion and have approved the final protocol manuscript.

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COMPETING INTERESTS

Professor Ian Hickie was an inaugural Commissioner on Australia's National Mental Health Commission (2012-18). He is the Co-Director, Health and Policy at the Brain and Mind Centre (BMC) University of Sydney. The BMC operates an early-intervention youth services at Camperdown under contract to headspace. Professor Hickie has previously led community-based and pharmaceutical industry-supported (Wyeth, Eli Lily, Servier, Pfizer, AstraZeneca) projects focused on the identification and better management of anxiety and depression. He was a member of the Medical Advisory Panel for Medibank Private until October 2017, a Board Member of Psychosis Australia Trust and a member of Veterans Mental Health Clinical Reference group. He is the Chief Scientific Advisor to, and a 5% equity shareholder in, InnoWell Pty Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the $30 M Australian Government-funded Project Synergy (2017-20; a three-year program for the transformation of mental health services) and to lead transformation of mental health services internationally through the use of innovative technologies.

A/Prof Elizabeth Scott is the Medical Director, Young Adult Mental Health Unit, St Vincent's Hospital Darlinghurst, Discipline Leader of Adult Mental Health, School of Medicine, University of Notre Dame, Research Affiliate, The University of Sydney and Consultant Psychiatrist. She has received honoraria for educational seminars related to the clinical management of depressive disorders supported by Servier and Eli-Lilly pharmaceuticals. She has participated in a national advisory board for the antidepressant compound Pristiq, manufactured by Pfizer. She was the National Coordinator of an antidepressant trial sponsored by Servier.

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Protocol for a Young Adult Mental Health (Uspace) Cohort: Personalising multidimensional care in young people admitted to hospital.

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Protocol for a Young Adult Mental Health (Uspace) Cohort: Personalising multidimensional care in young people admitted to hospital.

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ABSTRACT

Introduction Currently, the literature on personalised and measurement-based mental health care is inadequate with major gaps in the development and evaluation of 21St Century service models. Clinical presentations of mental ill health in young people are heterogeneous, and clinical and functional outcomes are often sub-optimal. Thus, treatments provided in a person-centered and responsive fashion are critical to meet the unique needs of young people and improve individual outcomes. Personalised care also requires concurrent assessment of factors relating to outcomes and underlying neurobiology. This study builds on a completed feasibility study and will be the first to incorporate clinical, cognitive, circadian, metabolic and hormonal profiling with personalised and measurement-based care in a cohort of young people admitted to hospital.

Methods and analysis This prospective, transdiagnostic, observational study will be offered to all young people between the ages of 16 and 30 years admitted to the inpatient unit of the participating centre. In total, 400 participants will be recruited. On admission to hospital, young people will undergo clinical and diagnostic assessment, cognitive testing, self-report questionnaires, metabolic and hormonal data collection, and anthropomorphic measurements. Participants will wear an actigraphy watch for at least one week during admission to measure circadian patterns and sleep-wake cycles. A feedback session between clinician and participant will occur after clinical and other laboratory assessments to tailor individual treatment plans, explain the ongoing process of measurement-based care, and provide participant and family education. Associations between cognitive impairments, disturbed sleep-wake behaviours, circadian rhythms, clinical symptoms, and functional impairments will be evaluated to improve the understanding of parameters affecting clinical outcomes.

Ethics and dissemination This study protocol was approved by the Human Research Ethics Committees of the University of Sydney (HREC USYD 2015/867) and St Vincent's Hospital (HREC SVH 17/045). This study will be published upon completion in a peer-reviewed journal.

ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS OF THIS STUDY:

- This study will follow a large cohort (n=400) of young people admitted to hospital for mental health care to examine determinants of clinically significant mental and physical health, and social, educational and occupational outcomes.
- As an observational study this will be naturalistic in fashion and no randomisation or control group will be included.
- The multifaceted variables collected such as anthropomorphic, metabolic, hormonal, cognitive, circadian and symptomatic data will offer information on the multifactorial variables leading to mental and physical ill health and treatment outcomes.
- Heterogeneity of the clinical presentations to an inpatient setting strengthens the study's generalisability to other similarly severe presentations of mental ill-health in young people.

KEYWORDS: Study protocol, observational study, affective disorder, young adult, mood and psychotic disorders, measurement based care, personalised care

INTRODUCTION

Clinical presentations of mental ill-health in young people are very heterogeneous in fashion. Current diagnostic criteria often fit poorly with the subthreshold or mixed presentations that are common in young people [1]. Typically, mental health care has relied on these diagnostic criteria to inform clinical decisions, leading to stereotyped and limited treatment responses which are often not well matched to individual needs. In accordance with a shift in health-care services and research priorities from evidence-based to personalised medicine [2], personalised, sequenced, multidisciplinary and more measurement-based interventions are new goals. These aim to translate evidence-based methodologies into individual treatment plans [2, 3]. Consequently, we have proposed a highly personalised and measurement-based care model for use in youth mental health services [4]. This transdiagnostic, person-centered model of care emphasises early access to personalised care through a comprehensive multidimensional assessment of various clinical and functional domains [5], including social and occupational functioning, self-harm and suicide risk, alcohol and substance misuse, physical health, clinical severity and stage (Stage 1a (non-specific symptoms) to Stage 4 (severe, persistent, and unremitting illness)) [6, 7], and illness subtypes (psychosis, anxious depression, bipolar spectrum). It also links with putative pathophysiological pathways (neurodevelopmental, hyperarousal, circadian) as well as individual illness trajectories [1, 8-10]. Such a clinical stage-appropriate and transdiagnostic framework may lead to improved clinical outcomes as it helps to guide the selection of treatments based on individual needs and symptom burden as well as underlying pathophysiological mechanisms [1].

Objectives of the Study and Conceptual Framework

The "Personalised Multidimensional Care" study will generate multidimensional – i.e. clinical, functional, cognitive, circadian, metabolic, and hormonal – profiles for participants with clinician feedback, specifically addressing individual issues affecting participant outcomes such as cognitive impairments, disturbed sleep-wake behaviours and circadian rhythms, clinical symptoms, and functional impairments.

The objectives of the study are:

- To establish a standardised measurement-based and personalised care research protocol in an inpatient unit

- To evaluate clinical parameters that impact participant outcomes such as cognitive impairments, disturbed sleep-wake behaviours and circadian rhythms, clinical symptoms, and functional impairments.
- To investigate associations between metabolic, hormonal, clinical, self-report, and circadian factors.
- To compare the inpatient cohort data with similar data from young people presenting to outpatient youth mental health services (e.g. Brain and Mind Centre cohorts [9, 11-13]).

Cognitive testing and circadian profiling is not yet often routinely available in standard clinical care but is very important in understanding the relationship between symptoms and functioning, as neuropsychological deficits and dysregulated sleep-wake cycles have been linked to poorer functional outcomes [8, 14-17].

Furthermore, incorporation of metabolic and hormonal profiles is imperative in capturing, evaluating and treating co-morbid and contributing conditions such as metabolic syndrome and polycystic ovarian syndrome (PCOS) which are often found concurrently in young psychiatric patients [18-21].

The "Personalised Multidimensional Care" study focuses on an inpatient young adult mental health clinic (Uspace). A key strength of this cohort is in its heterogeneity and ability to capture a presently severe hospitalised sample of young adults with varying mental disorders. The cohort will allow for studying a wide range of personalised interventions, whilst also examining the longitudinal trajectory of this young, more severely ill cohort, and the associations between detailed clinical, hormonal and metabolic profiles, social, neurocognitive, functional and circadian outcomes.

As previously demonstrated, the use of Health Information Technologies (HITs) (computerised, self-reported e-health technologies such as the InnoWell Platform (Project Synergy, InnoWell Pty Ltd) [22]) facilitates systematic multidimensional assessment in young people seeking help [23], enables opportune and timely responses from service providers and clinicians [23], and will, therefore, facilitate the development and delivery of highly personalised and measurement-based treatment plans.

The multidimensional assessments (clinical, functional, cognitive, circadian, metabolic, and hormonal) and resulting personalised interventions will enhance knowledge and inform clinical practice to improve standard clinical care in an inpatient unit. However, personalised care

means implementation of new protocols, training, and practice, as well as cultivating a new conceptual framework [24, 25]. We have previously shown that it is feasible to integrate technology and neurocognitive testing as standard clinical care in an inpatient unit, and that neurocognitive profiling may help us to better understand the illness severity in young patients [24]. Based on these results, we have decided to add further routine assessments (e.g., circadian, metabolic, and hormonal profiling) to be able to routinely provide personalised and measurement-based care. This study will integrate these approaches to help further knowledge in the field and facilitate translational changes to mental health care. Importantly, the personalised care approach based on multidimensional assessments is a collaborative approach and requires multidisciplinary teams of health professionals and involves shared decision-making based on the participant's best interests [25, 26].

METHODS AND ANALYSIS

Study design and setting

This prospective, transdiagnostic, observational study will offer recruitment to all inpatients aged 16-30 admitted to the Young Adult Mental Health Unit (Uspace), St Vincent's Private Hospital Sydney, Australia. Uspace is a voluntary private mental health service, targeted to the needs of young adults. Furthermore, it is a unique multidisciplinary clinical setting for research. Patients are referred for the assessment of mental health problems; with a mission to promote recovery and psychological well-being of young adults with severe and emerging mental health problems.

This "Personalised Multidimensional Care" study has started in March 2020 and will be conducted over a period of 5 years with assessments at baseline and possible longitudinal follow-up available upon participant consent up to 24 months. That is, with the patient's consent we will invite patients back for a follow-up study. At 24 months the assessments conducted at baseline will be repeated. This will inform a unique tracking of the patients from a inpatient facility. We are in the process of an ethics amendment to include an additional 6 month and 12 month follow-up to improve the care provided as we have found this to be effective in previous experience with other studies.

The recruitment will be based on the presentation to care and is not restricted by specific diagnostic criteria. The diagnosis-independent selection of participants as well as the

comprehensive assessments are consistent with the transdiagnostic 'Research Domain Criteria' (RDoC) approach [27]. RDoC aims to classify mental disorders based on neurobiological and behavioural measures that cut across current disorder categories. The use of functional, circadian, hormonal, metabolic, and cognitive assessments, allows to attain a comprehensive picture of the individuals admitted to USpace, and a subsequent classification based on biobehavioral dimensions. Furthermore, as this study is offered young people admitted to Uspace independent from diagnosis (i.e., we will not exclude young people with a primary diagnosis outside a target category, a co-morbid disorder or those who have some, but not all of the criteria required for a diagnosis of a specific disorder), our resulting cohort will have the appropriate variance as advocated by proponents of the RDoC approach [28]. However, the vast majority of young people admitted to USpace will have a primary diagnosis of an affective disorder. These include depressive disorder, anxiety disorder, bipolar disorder, or affective psychosis.

Participant and public involvement

The Health Information Technology (HIT) system (InnoWell Platform (InnoWell Pty Ltd) [22], which will be used for the collection of self-report data in the study, has been developed with participant and public involvement. Although young people were consulted during the development of the technology used to measure relevant outcomes of the study, they were not invited to comment on the study design. However, we will invite patient and public involvement representatives to help us writing a plain language summary of the results and developing our dissemination strategy.

Patient Cohort

Study participants are currently admitted young adult inpatients, aged 16-30, presenting with a severe affective episode (i.e. depressive, manic, anxious; including those with psychotic features). Diagnosis will be a consensus diagnosis; that is, via multidisciplinary clinical assessment (by psychiatrists, psychologists and allied health professionals).

Exclusion criteria for this study are: (i) insufficient fluency in the English language to participate in the cognitive testing; (ii) inability to consent due to intellectual impairment (for example, IQ < 70 as determined by the treating psychiatrist/psychologist) or severity of mental illness (as determined by the treating psychiatrist/psychologist); and (iii) refusal to provide informed consent.

Comorbid or pre-existing childhood-onset conditions (for example Attention Deficit Hyperactivity Disorder (ADHD) and conduct disorder), as well as alcohol or other substance misuse or autistic spectrum disorders are not exclusion criteria.

Study course and procedures

Potential participants who are admitted to USpace and interested in participating will be referred to the research study at arms-length. The participant will then be in-depth informed by the research staff based in the clinic to introduce the study and undertake consent. Through consecutive referral, eligible participants who are newly admitted to Uspace will be booked in to complete neurocognitive testing and self-report questionnaires after informed written consent. Participants' availability and booking schedule is based around their own routine appointments and groups as inpatients, with most participants being booked within four days of admission. Hormonal and metabolic measures are routinely collected at Uspace on admission as part of standard clinical care, this data will also be used for research purposes on and during admission as indicated by standard of care, regardless of entry into the study. Neurocognitive testing (CANTAB) is completed on a tablet devide, taking between 40 and 50 minutes. The self-report questionnaire will be completed the day after neurocognitive testing, taking approximately 45 to 60 minutes. Both, neurocognitive testing and the self-report questionnaire can be split and completed on two consecutive days. Actigraphy watches will be set up to record and given to patients to wear once informed consent is provided. Participants will wear the actigraphy watches during the admission period for a maximum of 14 days and a minimum of 6 days. No supervision is needed during wearing of the actiwatches. The appropriate clinician that admitted the corresponding participant during the admission process will complete a 'Clinical Assessment Form'. The multidimensional assessments as well as the feedback session will inform personalised interventions offered to the young adult participants in a shared decision-making process.

At follow-up, all assessments are repeated except for clinical assessment. Clinical assessment is only done in participants that are re-admitted to USpace within the follow up period.

An overview and timeline of the assessments is provided in Table 1.

Table 1: Timeline and overview of assessments after providing written informed consent. A feedback session is offered routinely and will be organised after completion of the assessments.

	Baseline			**Follow-Up (6 months)***			**Follow-Up (12 months)***			**Follow-Up (24 month)***		
	First 24-48 h	Within 7 days	Within 14 days	First 24-48 h	Within 7 days	Within 14 days	First 24-48 h	Within 7 days	Within 14 days	First 24-48 h	Within 7 days	Within 14 days
Routine assessments												
Blood withdrawal to assess hormonal and metabolic profiles	X			X			X			X		
Clinical Assessment	X			X			X			X		
Neurocognitive screening (CANTAB, 40-50 min)	X			X			X			X		
Actigraphy setup for circadian profiling (duration of the profiling: 6-14 days)	X			X			X			X		
Feedback Session (CANTAB, clinical assessments)		X			X			X			X	
Feedback Session (Actigraphy)			X			X			X			X
Additional asssessments												
Self report questionnaire (45 to 60 min)		X			X			X			X	

* We are in the process of an ethics amendment to include an additional 6 month and 12 month follow-up to improve the care provided. Clinical assessment is only done in participants that are re-admitted to USpace within the follow up period.

Assessments

Clinical Presentation

The clinical presentation is captured in the 'Clinical Assessment Form'. In addition, this form records information regarding the participants current episode/presentation, psychiatric history, medical history, social and occupational functioning, clinical severity/improvement and clinical stage.

In addition, menstrual history and symptoms are assessed in the female population using a self-report questionnaire capturing age of menarche, regularity of the period, amenorrhoea, period pain, body hair, skin, mood, sleep and fatigue symptoms.

Self-report Questionnaire

The self-report questionnaire is implemented within HIT system (InnoWell Platform (InnoWell Pty Ltd) [22] and is, thus, electronically completed on a touchscreen device (e.g. tablet device). It captures key clinical information regarding the following:

Demographics

Biological sex is specified, and age is calculated. Current engagement in part- or full-time education or employment is recorded to determine Not in Education, Employment, or Training (NEET) status. NEET is assigned if there is no full- or part-time education, employment, training, or volunteer work. Current receipt of any government benefits is also recorded.

Personal Mental Illness History

Known childhood-onset disorders (i.e. with clear onset prior to 12 years old) are recorded in addition to current diagnoses.

Family History of Mental Illness

Known family history of mental illness in first degree relatives is recorded.

Treatment Utilisation/History

Exposure to classes of medication (antidepressant, antipsychotic, mood stabiliser, or stimulant medication), and hospitalisation overnight or longer due to a mental health problem (including specification of hospitalisation due to illness severity or suicidality) are recorded.

Alcohol and Substance Use

The presence of any reported use of tobacco, alcohol, cannabis, stimulants, or other drugs is recorded.

Clinical Symptoms

Initial questions obtain key demographic and clinical information, focusing on critical illness course variables (for example, onset of symptoms, hospitalizations, age of first help seeking). Standardised questionnaires include the 10-item Kessler Psychological Distress Scale (K-10) [29] to detect psychological distress, with scores ranging between 10 and 50 (a score over 30 representing a likely severe mental disorder); Quick Inventory of Depressive Symptomatology (QIDS-16) [30] to assess severity of depressive symptoms, with scores ranging between 1 and 27 (a higher score representing greater severity of depression); Overall Anxiety Severity and Impairment Scale (OASIS), a 5-item measure for assessment of severity and impairment in regard to anxiety symptoms [31], with scores ranging between 0 and 20 (a higher score representing a higher frequency and severity of anxiety (across anxiety disorders); Psychosis Screener derived from Community Assessment of Psychic Experiences (CAPE)[32], a positive symptoms scale and psychosis screener, developed to measure the lifetime prevalence of psychotic-like experiences in the general population; Hypomania Screener derived from the Altman Self-Rating Mania Scale (ASRM) [33], a 5-item self-rating scale to assess the severity of manic symptoms, a higher score (five or more) indicating a high probability of a manic or hypomanic condition; Suicidal Ideation Attributes Scale (SIDAS) [34], a 5-item scale to screen participants for suicidal thoughts and severity of these thoughts, with scores ranging between 0 and 50 (a higher score representing more severe suicidal thoughts (a score over 21 being in the high risk category); and, the Somatic and Psychological Health Report (SPHERE-12) [35], a 12-item measure to screen for current depression and/or anxiety-like symptoms (a score of two or more on the psychological subscale and a score of three or more on the somatic subscale indicating current depression and/or anxiety-like symptoms).

Neurocognitive Screening

Self-reported, non-structured, standardised questions in regard to the participant's own sense of cognition will be assessed prior to testing (for example, changes in everyday thinking skills and neurocognitive abilities).

A trained research psychologist or psychiatric registrar at Uspace will administer the cognitive testing battery, which includes computerized assessments. First, premorbid intellectual functioning ('predicted IQ') is estimated on the basis of performance on the Wechsler Test of Adult Reading[36]. Following this, participants complete tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB)[37] on an HIT platform. CANTAB tests have the advantage of being largely non-verbal (i.e. language-independent, culture-free) and have been described in detail elsewhere [37-39]. Five tasks are included in this study: the Motor Screening Task (MOT), an introductory task to prepare participants for testing (i.e. not included in overall results) using induction of sensorimotor and comprehension; the Verbal Recognition Memory task (VRM immediate and recall/delayed) assessing 'verbal memory and new learning' indexed by the encoding and subsequent retrieval of verbal information scores; the Attention Switching Task (AST) assessing 'mental flexibility' and indexed by the total adjusted score; the Paired Association Learning task (PAL) assessing 'visuo-spatial learning and memory' indexed by the total adjusted errors score from; and, the Rapid Visual Processing task (RVP) assessing 'sustained attention' and indexed by the RVP A prime (sensitivity to the target).

Participants' individual, normed results are calculated by a trained research psychologist within two to three days of completion of cognitive testing battery. Calculation of CANTAB z-scores are completed for each participant. While each participant's predicted IQ is assessed in the cognitive screener, this is specifically to personalize results based on each participant's age, education and background, compared to 'demographically corrected' standardised scores (z-scores) using an internal normative database of healthy controls (http://www.camocog.com).

Sleep-Wake Cycle/Circadian Profile

Participants are given an actigraphy watch (GENEActiv watch, Activinsights Ltd., Kimbolton, UK) to wear on the non-dominant wrist during the admission period for a maximum of 14 days and a minimum of 6 days. This actigraph records motor activity levels, skin temperature, and ambient light exposure continuously at a rate of 30hz for the duration of the recording period. The GENEActiv devices have been validated against several types of accelerometry-based activity monitors[40-42] as well as for sleep-wake scoring [43]. More specifically, sleep-wake detection in data collected with the GENEActiv devices has been found to have strong reliability and validity when compared to data collected with other GENEActiv monitors or with Actiwatch Spectrum devices (a well-established instrument in sleep and circadian research) [43]. For over three decades, actigraphy monitors like the GENEActiv devices have

been considered as non-invasive instruments to measure sleep and activity patterns and have been used extensively for research purposes in diverse clinical settings including: sleep disorders, various medical illnesses (e.g. cancer, HIV, traumatic brain injuries, neurodegenerative diseases) and mental disorders (e.g. anxiety, depression, bipolar and psychotic disorders).

Metabolic and hormonal profiles

As standard clinical care, metabolic data, including measures of body, weight, waist circumference, as well as blood pressure readings and routine metabolic bloods (including e.g. glucose, insulin, cholesterol, low- and high-density lipoprotein, triglycerides etc.) are routinely collected at Uspace on admission, this data will be used for research purposes. After assessment by a clinician, women with clinical evidence of co-morbid polycystic ovarian syndrome (PCOS) will undergo further hormonal assays (including e.g. oestradiol, Dehydroepiandrosterone Sulfate, Anti Mullerian Hormone) collected as standard clinical care.

Feedback and personalised care

Once both the self-report questionnaire and cognitive testing have been completed by the participant, and the clinical assessment form has been completed by the admitting clinician, a feedback report will be generated (within 7 days of the completed assessments). A brief feedback session will be organised with the participant in order to go through and explain results and what that means in terms of more personalised intervention. This feedback report and session will be between the participant, treating clinician and clinical researcher. The feedback session will be part of the standard clinical care whereby the results of the testing will be explained in detail to the participant, management options will be explored, and any questions the participant may have will be addressed; furthermore, briefing will occur during the participant's weekly clinical reviews. The feedback session aims to give the participant a better understanding of certain aspects of their mental health and wellbeing and what they, and their clinicians, can do to improve those areas. A feedback report of the actigraphy (sleep-wake cycle and circadian) assessment results will be provided to the clinician upon completion of the total time (maximum 14 days) wearing the actigraphy watch.

The results of the multidimensional assessments – including clinical, functional, cognitive, circadian, metabolic, and hormonal profiles – as well as the feedback session will inform

personalised interventions offered to the young adult participant in a shared decision-making process.

Sample size calculation

We aim to include 400 participants annually, based on our knowledge typically 700-800 inpatients are admitted to Uspace per year. Thus, we expect to be able to collect data from 2,000 participants over the period of the study. Although patient retention in youth mental health services is difficult to predict [44], in our experience, 70% of inpatients are retained from baseline and throughout follow-up assessments. This has been accounted for in our sample size estimation.

Data analysis plan

Once completed, the data from the self-report assessment is collated, and displays a detailed and immediate dashboard of results. This information is available to a trained research psychologist immediately upon the participant's completion of the self-report assessment and will be used to prepare the feedback report.

This "Personalised Multidimensional Care" study allows for the assessment of multidimensional – i.e. clinical, functional, cognitive, circadian, metabolic, and hormonal – profiles for young adult participants. This includes:

- Evaluating parameters affecting participant outcomes such as cognitive impairments, disturbed sleep-wake behaviours and circadian rhythms, clinical symptoms, and functional impairments.
- Investigating associations between metabolic, hormonal, clinical, self-report, and circadian factors.
- Comparisons with similar data from young people presenting to outpatient youth mental health services (e.g. Brain and Mind Centre cohorts [9, 11-13]).

As the data collected will be highly multidimensional, aside from the use of standard statistical approaches (e.g. ANOVA, correlations, regression), we will employ more advanced statistical techniques to investigate the underlying interactions between demographics, clinical presentation, neurocognition, sleep-wake profiles, and metabolics profiles in driving mental and physical ill-health. These approaches include mixed-effects modelling as this is suited to data where samples are observed repeatedly, Bayesian modelling as this can be used to estimate

the level of uncertainity in our parameter estimations [45, 46], structural equation modelling [47], and more data-driven techniques [48-50] such as hierarchical cluster analysis [15, 24, 51], latent profile analysis [52], and group-based trajectory modelling [53] will be applied. To take advantage of the multidimensional and longitudinal nature of the data collected, machine learning approaches can be used to build models predictive, at baseline, of downstream physical and mental ill-health outcomes. Algorithms that also provide some transparency in variable importance such as tree-based algorithms (Random Forest, XGBoost) and penalised regression (LASSO, Elastic-net) will be suitable for this.

To handle missing data points, we will also use (i) maximum likelihood approaches as these can estimate the most likely value of a parameter based on the observed data points, and (ii) multiple imputation to generate multiple imputed datasets where each dataset is analysed separately and the results are pooled. This approach ascertains the sensitivity of the statistical analysis based on different imputation estimates.

ETHICS AND DISSEMINATION

This study protocol was approved by the University of Sydney (HREC USYD 2015/867) and St Vincent's Hospital Human Research Ethics Committees (HREC SVH 17/045). Following confirmation that potential participants from the Uspace inpatient cohort are of mental and intellectual capacity to give informed consent, and have no language barriers, a complete description of the study will be discussed and eligible participants will be given a Participant Information Sheet and Consent Form and followed-up by the researcher for informed written consent, no less than 24 hours later, with those under the age of 18 having their parent or guardian also consent. This study is minimally invasive, and any adverse outcomes will inform procedure.

All participant data will be de-identified and stored in accordance with applicable security standards; therefore, the privacy of all participants will be protected.

The research findings will be disseminated through publications in peer-reviewed journals and conference proceedings, and participant data will be non-identifiable.

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CONTRIBUTORS

IBH and EMS conceived the research idea, designed the study, and are the principal investigators (for corresponding sites); AMT contributed to study conception, wrote the study protocol with input of JSC (actigraphy), AG (hormonal and metabolic measurements), KH, LP, and EMS. AMT manages the study with input of EMS, KH, and LP. EMS contributes to clinical organization; KH and LP manage patient unit participation and supervision. AMT wrote the first draft of the manuscript; CR, AG and YJCS contributed to major edits in later versions. All authors contributed to discussion and have approved the final protocol manuscript.

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COMPETING INTERESTS

Professor Ian Hickie was an inaugural Commissioner on Australia's National Mental Health Commission (2012-18). He is the Co-Director, Health and Policy at the Brain and Mind Centre (BMC) University of Sydney. The BMC operates an early-intervention youth services at Camperdown under contract to headspace. Professor Hickie has previously led community-based and pharmaceutical industry-supported (Wyeth, Eli Lily, Servier, Pfizer, AstraZeneca) projects focused on the identification and better management of anxiety and depression. He was a member of the Medical Advisory Panel for Medibank Private until October 2017, a Board Member of Psychosis Australia Trust and a member of Veterans Mental Health Clinical Reference group. He is the Chief Scientific Advisor to, and a 5% equity shareholder in, InnoWell Pty Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the $30 M Australian Government-funded Project Synergy

(2017-20; a three-year program for the transformation of mental health services) and to lead transformation of mental health services internationally through the use of innovative technologies.

A/Prof Elizabeth Scott is the Medical Director, Young Adult Mental Health Unit, St Vincent's Hospital Darlinghurst, Discipline Leader of Adult Mental Health, School of Medicine, University of Notre Dame, Research Affiliate, The University of Sydney and Consultant Psychiatrist. She has received honoraria for educational seminars related to the clinical management of depressive disorders supported by Servier and Eli-Lilly pharmaceuticals. She has participated in a national advisory board for the antidepressant compound Pristiq, manufactured by Pfizer. She was the National Coordinator of an antidepressant trial sponsored by Servier.

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Protocol for a Young Adult Mental Health (Uspace) Cohort: Personalising multidimensional care in young people admitted to hospital.

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ABSTRACT

Introduction Currently, the literature on personalised and measurement-based mental health care is inadequate with major gaps in the development and evaluation of 21St Century service models. Clinical presentations of mental ill health in young people are heterogeneous, and clinical and functional outcomes are often sub-optimal. Thus, treatments provided in a person-centered and responsive fashion are critical to meet the unique needs of young people and improve individual outcomes. Personalised care also requires concurrent assessment of factors relating to outcomes and underlying neurobiology. This study builds on a completed feasibility study and will be the first to incorporate clinical, cognitive, circadian, metabolic and hormonal profiling with personalised and measurement-based care in a cohort of young people admitted to hospital.

Methods and analysis This prospective, transdiagnostic, observational study will be offered to all young people between the ages of 16 and 30 years admitted to the inpatient unit of the participating centre. In total, 400 participants will be recruited. On admission to hospital, young people will undergo clinical and diagnostic assessment, cognitive testing, self-report questionnaires, metabolic and hormonal data collection, and anthropomorphic measurements. Participants will wear an actigraphy watch for at least one week during admission to measure circadian patterns and sleep-wake cycles. A feedback session between clinician and participant will occur after clinical and other laboratory assessments to tailor individual treatment plans, explain the ongoing process of measurement-based care, and provide participant and family education. Associations between cognitive impairments, disturbed sleep-wake behaviours, circadian rhythms, clinical symptoms, and functional impairments will be evaluated to improve the understanding of parameters affecting clinical outcomes.

Ethics and dissemination This study protocol was approved by the Human Research Ethics Committees of the University of Sydney (HREC USYD 2015/867) and St Vincent's Hospital (HREC SVH 17/045). This study will be published upon completion in a peer-reviewed journal.

ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS OF THIS STUDY:

- This study will follow a large cohort (n=400) of young people admitted to hospital for mental health care to examine determinants of clinically significant mental and physical health, and social, educational and occupational outcomes.
- As an observational study this will be naturalistic in fashion and no randomisation or control group will be included.
- The multifaceted variables collected such as anthropomorphic, metabolic, hormonal, cognitive, circadian and symptomatic data will offer information on the multifactorial variables leading to mental and physical ill health and treatment outcomes.
- Heterogeneity of the clinical presentations to an inpatient setting strengthens the study's generalisability to other similarly severe presentations of mental ill-health in young people.

KEYWORDS: Study protocol, observational study, affective disorder, young adult, mood and psychotic disorders, measurement based care, personalised care

INTRODUCTION

Clinical presentations of mental ill-health in young people are very heterogeneous in fashion. Current diagnostic criteria often fit poorly with the subthreshold or mixed presentations that are common in young people [1]. Typically, mental health care has relied on these diagnostic criteria to inform clinical decisions, leading to stereotyped and limited treatment responses which are often not well matched to individual needs. In accordance with a shift in health-care services and research priorities from evidence-based to personalised medicine [2], personalised, sequenced, multidisciplinary and more measurement-based interventions are new goals. These aim to translate evidence-based methodologies into individual treatment plans [2, 3]. Consequently, we have proposed a highly personalised and measurement-based care model for use in youth mental health services [4]. This transdiagnostic, person-centered model of care emphasises early access to personalised care through a comprehensive multidimensional assessment of various clinical and functional domains [5], including social and occupational functioning, self-harm and suicide risk, alcohol and substance misuse, physical health, clinical severity and stage (Stage 1a (non-specific symptoms) to Stage 4 (severe, persistent, and unremitting illness)) [6, 7], and illness subtypes (psychosis, anxious depression, bipolar spectrum). It also links with putative pathophysiological pathways (neurodevelopmental, hyperarousal, circadian) as well as individual illness trajectories [1, 8-10]. Such a clinical stage-appropriate and transdiagnostic framework may lead to improved clinical outcomes as it helps to guide the selection of treatments based on individual needs and symptom burden as well as underlying pathophysiological mechanisms [1].

Objectives of the Study and Conceptual Framework

The "Personalised Multidimensional Care" study will generate multidimensional – i.e. clinical, functional, cognitive, circadian, metabolic, and hormonal – profiles for participants with clinician feedback, specifically addressing individual issues affecting participant outcomes such as cognitive impairments, disturbed sleep-wake behaviours and circadian rhythms, clinical symptoms, and functional impairments.

The objectives of the study are:

- To establish a standardised measurement-based and personalised care research protocol in an inpatient unit

- To evaluate clinical parameters that impact participant outcomes such as cognitive impairments, disturbed sleep-wake behaviours and circadian rhythms, clinical symptoms, and functional impairments.
- To investigate associations between metabolic, hormonal, clinical, self-report, and circadian factors.
- To compare the inpatient cohort data with similar data from young people presenting to outpatient youth mental health services (e.g. Brain and Mind Centre cohorts [9, 11-13]).

Cognitive testing and circadian profiling is not yet often routinely available in standard clinical care but is very important in understanding the relationship between symptoms and functioning, as neuropsychological deficits and dysregulated sleep-wake cycles have been linked to poorer functional outcomes [8, 14-17].

Furthermore, incorporation of metabolic and hormonal profiles is imperative in capturing, evaluating and treating co-morbid and contributing conditions such as metabolic syndrome and polycystic ovarian syndrome (PCOS) which are often found concurrently in young psychiatric patients [18-21].

The "Personalised Multidimensional Care" study focuses on an inpatient young adult mental health clinic (Uspace). A key strength of this cohort is in its heterogeneity and ability to capture a presently severe hospitalised sample of young adults with varying mental disorders. The cohort will allow for studying a wide range of personalised interventions, whilst also examining the longitudinal trajectory of this young, more severely ill cohort, and the associations between detailed clinical, hormonal and metabolic profiles, social, neurocognitive, functional and circadian outcomes.

As previously demonstrated, the use of Health Information Technologies (HITs) (computerised, self-reported e-health technologies such as the InnoWell Platform (Project Synergy, InnoWell Pty Ltd) [22]) facilitates systematic multidimensional assessment in young people seeking help [23], enables opportune and timely responses from service providers and clinicians [23], and will, therefore, facilitate the development and delivery of highly personalised and measurement-based treatment plans.

The multidimensional assessments (clinical, functional, cognitive, circadian, metabolic, and hormonal) and resulting personalised interventions will enhance knowledge and inform clinical practice to improve standard clinical care in an inpatient unit. However, personalised care

means implementation of new protocols, training, and practice, as well as cultivating a new conceptual framework [24, 25]. We have previously shown that it is feasible to integrate technology and neurocognitive testing as standard clinical care in an inpatient unit, and that neurocognitive profiling may help us to better understand the illness severity in young patients [24]. Based on these results, we have decided to add further routine assessments (e.g., circadian, metabolic, and hormonal profiling) to be able to routinely provide personalised and measurement-based care. This study will integrate these approaches to help further knowledge in the field and facilitate translational changes to mental health care. Importantly, the personalised care approach based on multidimensional assessments is a collaborative approach and requires multidisciplinary teams of health professionals and involves shared decision-making based on the participant's best interests [25, 26].

METHODS AND ANALYSIS

Study design and setting

This prospective, transdiagnostic, observational study will offer recruitment to all inpatients aged 16-30 admitted to the Young Adult Mental Health Unit (Uspace), St Vincent's Private Hospital Sydney, Australia. Uspace is a voluntary private mental health service, targeted to the needs of young adults. Furthermore, it is a unique multidisciplinary clinical setting for research. Patients are referred for the assessment of mental health problems; with a mission to promote recovery and psychological well-being of young adults with severe and emerging mental health problems.

This "Personalised Multidimensional Care" study has started in March 2020 and will be conducted over a period of 5 years with assessments at baseline and possible longitudinal follow-up available upon participant consent up to 24 months (estimated end date of recruitment: March 2023; estimated date of study completion: March 2025). That is, with the patient's consent, we will invite patients back for a follow-up assessment. At 24 months the assessments conducted at baseline will be repeated. This will inform a unique tracking of the patients from an inpatient facility. We are in the process of an ethics amendment to include an additional 6 month and 12 month follow-up to improve the care provided as we have found this to be effective in previous experience with other studies.

The recruitment will be based on the presentation to care and is not restricted by specific diagnostic criteria. The diagnosis-independent selection of participants as well as the comprehensive assessments are consistent with the transdiagnostic 'Research Domain Criteria' (RDoC) approach [27]. RDoC aims to classify mental disorders based on neurobiological and behavioural measures that cut across current disorder categories. The use of functional, circadian, hormonal, metabolic, and cognitive assessments, allows to attain a comprehensive picture of the individuals admitted to USpace, and a subsequent classification based on biobehavioral dimensions. Furthermore, as this study is offered young people admitted to Uspace independent from diagnosis (i.e., we will not exclude young people with a primary diagnosis outside a target category, a co-morbid disorder or those who have some, but not all of the criteria required for a diagnosis of a specific disorder), our resulting cohort will have the appropriate variance as advocated by proponents of the RDoC approach [28]. However, the vast majority of young people admitted to USpace will have a primary diagnosis of an affective disorder. These include depressive disorder, anxiety disorder, bipolar disorder, or affective psychosis.

Participant and public involvement

The Health Information Technology (HIT) system (InnoWell Platform (InnoWell Pty Ltd) [22], which will be used for the collection of self-report data in the study, has been developed with participant and public involvement. Although young people were consulted during the development of the technology used to measure relevant outcomes of the study, they were not invited to comment on the study design. However, we will invite patient and public involvement representatives to help us writing a plain language summary of the results and developing our dissemination strategy.

Patient Cohort

Study participants are currently admitted young adult inpatients, aged 16-30, presenting with a severe affective episode (i.e. depressive, manic, anxious; including those with psychotic features). Diagnosis will be a consensus diagnosis; that is, via multidisciplinary clinical assessment (by psychiatrists, psychologists and allied health professionals).

Exclusion criteria for this study are: (i) insufficient fluency in the English language to participate in the cognitive testing; (ii) inability to consent due to intellectual impairment (for example, IQ < 70 as determined by the treating psychiatrist/psychologist) or severity of mental

illness (as determined by the treating psychiatrist/psychologist); and (iii) refusal to provide informed consent.

Comorbid or pre-existing childhood-onset conditions (for example Attention Deficit Hyperactivity Disorder (ADHD) and conduct disorder), as well as alcohol or other substance misuse or autistic spectrum disorders are not exclusion criteria.

Study course and procedures

Potential participants who are admitted to USpace and interested in participating will be referred to the research study at arms-length to ensure that there is minimal perceived coercion from the referring clinician to the participant to participate in the study. The participant will then be in-depth informed by the research staff based in the clinic to introduce the study and undertake consent. Through consecutive referral, eligible participants who are newly admitted to Uspace will be booked in to complete neurocognitive testing and self-report questionnaires after informed written consent. Participants' availability and booking schedule is based around their own routine appointments and groups as inpatients, with most participants being booked within four days of admission. Hormonal and metabolic measures are routinely collected at Uspace on admission as part of standard clinical care, this data will also be used for research purposes on and during admission as indicated by standard of care, regardless of entry into the study. Neurocognitive testing (CANTAB) is completed on a tablet devide, taking between 40 and 50 minutes. The self-report questionnaire will be completed the day after neurocognitive testing, taking approximately 45 to 60 minutes. Both, neurocognitive testing and the self-report questionnaire can be split and completed on two consecutive days. Actigraphy watches will be set up to record and given to patients to wear once informed consent is provided. Participants will wear the actigraphy watches during the admission period for a maximum of 14 days and a minimum of 6 days. No supervision is needed during wearing of the actiwatches. The appropriate clinician that admitted the corresponding participant during the admission process will complete a 'Clinical Assessment Form'. The multidimensional assessments as well as the feedback session will inform personalised interventions offered to the young adult participants in a shared decision-making process.

At follow-up, all assessments are repeated except for clinical assessment, as we expect that the follow-up assessments will be conducted after discharge in almost all cases,. Therefore, the clinical assessment is only done in participants re-admitted to USpace within the follow-up period.

An overview and timeline of the assessments is provided in Table 1.

Table 1: Timeline and overview of assessments after providing written informed consent. A feedback session is offered routinely and will be organised after completion of the assessments.

	Baseline			**Follow-Up (6 months)***			**Follow-Up (12 months)***			**Follow-Up (24 month)***		
	First 24-48 h	Within 7 days	Within 14 days	First 24-48 h	Within 7 days	Within 14 days	First 24-48 h	Within 7 days	Within 14 days	First 24-48 h	Within 7 days	Within 14 days
Standard routine assessments												
Blood withdrawal to assess hormonal and metabolic profiles	X			X			X			X		
Clinical Assessment	X			X			X			X		
Neurocognitive screening (CANTAB, 40-50 min)	X			X			X			X		
Actigraphy setup for circadian profiling (duration of the profiling: 6-14 days)	X			X			X			X		
Feedback Session (CANTAB, clinical assessments)		X			X			X			X	
Feedback Session (Actigraphy)			X			X			X			X
Additional asssessments												
Self report questionnaire (45 to 60 min)		X			X			X			X	

* We are in the process of an ethics amendment to include an additional 6 month and 12 month follow-up to improve the care provided. Clinical assessment is only done in participants that are re-admitted to USpace within the follow up period.

Assessments

Clinical Presentation

The clinical presentation is captured in the 'Clinical Assessment Form'. In addition, this form records information regarding the participants current episode/presentation, psychiatric history, medical history, social and occupational functioning, clinical severity/improvement and clinical stage.

In addition, menstrual history and symptoms are assessed in the female population using a self-report questionnaire capturing age of menarche, regularity of the period, amenorrhoea, period pain, body hair, skin, mood, sleep and fatigue symptoms.

Self-report Questionnaire

The self-report questionnaire is implemented within HIT system (InnoWell Platform (InnoWell Pty Ltd) [22] and is, thus, electronically completed on a touchscreen device (e.g. tablet device). It captures key clinical information regarding the following:

Demographics

Biological sex is specified, and age is calculated. Current engagement in part- or full-time education or employment is recorded to determine Not in Education, Employment, or Training (NEET) status. NEET is assigned if there is no full- or part-time education, employment, training, or volunteer work. Current receipt of any government benefits is also recorded.

Personal Mental Illness History

Known childhood-onset disorders (i.e. with clear onset prior to 12 years old) are recorded in addition to current diagnoses.

Family History of Mental Illness

Known family history of mental illness in first degree relatives is recorded.

Treatment Utilisation/History

Exposure to classes of medication (antidepressant, antipsychotic, mood stabiliser, or stimulant medication), and hospitalisation overnight or longer due to a mental health problem (including specification of hospitalisation due to illness severity or suicidality) are recorded.

Alcohol and Substance Use

The presence of any reported use of tobacco, alcohol, cannabis, stimulants, or other drugs is recorded.

Clinical Symptoms

Initial questions obtain key demographic and clinical information, focusing on critical illness course variables (for example, onset of symptoms, hospitalizations, age of first help seeking). Standardised questionnaires include the 10-item Kessler Psychological Distress Scale (K-10) [29] to detect psychological distress, with scores ranging between 10 and 50 (a score over 30 representing a likely severe mental disorder); Quick Inventory of Depressive Symptomatology (QIDS-16) [30] to assess severity of depressive symptoms, with scores ranging between 1 and 27 (a higher score representing greater severity of depression); Overall Anxiety Severity and Impairment Scale (OASIS), a 5-item measure for assessment of severity and impairment in regard to anxiety symptoms [31], with scores ranging between 0 and 20 (a higher score representing a higher frequency and severity of anxiety (across anxiety disorders); Psychosis Screener derived from Community Assessment of Psychic Experiences (CAPE)[32], a positive symptoms scale and psychosis screener, developed to measure the lifetime prevalence of psychotic-like experiences in the general population; Hypomania Screener derived from the Altman Self-Rating Mania Scale (ASRM) [33], a 5-item self-rating scale to assess the severity of manic symptoms, a higher score (five or more) indicating a high probability of a manic or hypomanic condition; Suicidal Ideation Attributes Scale (SIDAS) [34], a 5-item scale to screen participants for suicidal thoughts and severity of these thoughts, with scores ranging between 0 and 50 (a higher score representing more severe suicidal thoughts (a score over 21 being in the high risk category); and, the Somatic and Psychological Health Report (SPHERE-12) [35], a 12-item measure to screen for current depression and/or anxiety-like symptoms (a score of two or more on the psychological subscale and a score of three or more on the somatic subscale indicating current depression and/or anxiety-like symptoms).

Neurocognitive Screening

Self-reported, non-structured, standardised questions in regard to the participant's own sense of cognition will be assessed prior to testing (for example, changes in everyday thinking skills and neurocognitive abilities).

A trained research psychologist or psychiatric registrar at Uspace will administer the cognitive testing battery, which includes computerized assessments. First, premorbid intellectual functioning ('predicted IQ') is estimated on the basis of performance on the Wechsler Test of Adult Reading[36]. Following this, participants complete tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB)[37] on an HIT platform. CANTAB tests have the advantage of being largely non-verbal (i.e. language-independent, culture-free) and have been described in detail elsewhere [37-39]. Five tasks are included in this study: the Motor Screening Task (MOT), an introductory task to prepare participants for testing (i.e. not included in overall results) using induction of sensorimotor and comprehension; the Verbal Recognition Memory task (VRM immediate and recall/delayed) assessing 'verbal memory and new learning' indexed by the encoding and subsequent retrieval of verbal information scores; the Attention Switching Task (AST) assessing 'mental flexibility' and indexed by the total adjusted score; the Paired Association Learning task (PAL) assessing 'visuo-spatial learning and memory' indexed by the total adjusted errors score from; and, the Rapid Visual Processing task (RVP) assessing 'sustained attention' and indexed by the RVP A prime (sensitivity to the target).

Participants' individual, normed results are calculated by a trained research psychologist within two to three days of completion of cognitive testing battery. Calculation of CANTAB z-scores are completed for each participant. While each participant's predicted IQ is assessed in the cognitive screener, this is specifically to personalize results based on each participant's age, education and background, compared to 'demographically corrected' standardised scores (z-scores) using an internal normative database of healthy controls (http://www.camocog.com).

Sleep-Wake Cycle/Circadian Profile

Participants are given an actigraphy watch (GENEActiv watch, Activinsights Ltd., Kimbolton, UK) to wear on the non-dominant wrist during the admission period for a maximum of 14 days and a minimum of 6 days. This actigraph records motor activity levels, skin temperature, and ambient light exposure continuously at a rate of 30hz for the duration of the recording period. The GENEActiv devices have been validated against several types of accelerometry-based activity monitors[40-42] as well as for sleep-wake scoring [43]. More specifically, sleep-wake detection in data collected with the GENEActiv devices has been found to have strong reliability and validity when compared to data collected with other GENEActiv monitors or with Actiwatch Spectrum devices (a well-established instrument in sleep and circadian research) [43]. For over three decades, actigraphy monitors like the GENEActiv devices have

been considered as non-invasive instruments to measure sleep and activity patterns and have been used extensively for research purposes in diverse clinical settings including: sleep disorders, various medical illnesses (e.g. cancer, HIV, traumatic brain injuries, neurodegenerative diseases) and mental disorders (e.g. anxiety, depression, bipolar and psychotic disorders).

Metabolic and hormonal profiles

As standard clinical care, metabolic data, including measures of body, weight, waist circumference, as well as blood pressure readings and routine metabolic bloods (including e.g. glucose, insulin, cholesterol, low- and high-density lipoprotein, triglycerides etc.) are routinely collected at Uspace on admission, this data will be used for research purposes. After assessment by a clinician, women with clinical evidence of co-morbid polycystic ovarian syndrome (PCOS) will undergo further hormonal assays (including e.g. oestradiol, Dehydroepiandrosterone Sulfate, Anti Mullerian Hormone) collected as standard clinical care.

Feedback and personalised care

Once both the self-report questionnaire and cognitive testing have been completed by the participant, and the clinical assessment form has been completed by the admitting clinician, a feedback report will be generated (within 7 days of the completed assessments). A brief feedback session will be organised with the participant in order to go through and explain results and what that means in terms of more personalised intervention. This feedback report and session will be between the participant, treating clinician and clinical researcher. The feedback session will be part of the standard clinical care whereby the results of the testing will be explained in detail to the participant, management options will be explored, and any questions the participant may have will be addressed; furthermore, briefing will occur during the participant's weekly clinical reviews. The feedback session aims to give the participant a better understanding of certain aspects of their mental health and wellbeing and what they, and their clinicians, can do to improve those areas. A feedback report of the actigraphy (sleep-wake cycle and circadian) assessment results will be provided to the clinician upon completion of the total time (maximum 14 days) wearing the actigraphy watch.

The results of the multidimensional assessments – including clinical, functional, cognitive, circadian, metabolic, and hormonal profiles – as well as the feedback session will inform

personalised interventions offered to the young adult participant in a shared decision-making process.

Sample size calculation

We aim to include 400 participants annually, based on our knowledge typically 700-800 inpatients are admitted to Uspace per year. Thus, we expect to be able to collect data from 2,000 participants over the period of the study. Although patient retention in youth mental health services is difficult to predict [44], in our experience, 70% of inpatients are retained from baseline and throughout follow-up assessments. This has been accounted for in our sample size estimation.

Data analysis plan

Once the participants have completed the self-report assessment, the data is collated and displayed as a detailed and immediate dashboard of results. This information is available to a trained research psychologist immediately upon the participant's completion of the self-report assessment and will be used to prepare the feedback report.

This "Personalised Multidimensional Care" study allows for the assessment of multidimensional – i.e. clinical, functional, cognitive, circadian, metabolic, and hormonal – profiles for young adult participants. This includes:

- Evaluating parameters affecting participant outcomes such as cognitive impairments, disturbed sleep-wake behaviours and circadian rhythms, clinical symptoms, and functional impairments.
- Investigating associations between metabolic, hormonal, clinical, self-report, and circadian factors.
- Comparisons with similar data from young people presenting to outpatient youth mental health services (e.g. Brain and Mind Centre cohorts [9, 11-13]).

As the data collected will be highly multidimensional, aside from the use of standard statistical approaches (e.g. ANOVA, correlations, regression), we will employ more advanced statistical techniques to investigate the underlying interactions between demographics, clinical presentation, neurocognition, sleep-wake profiles, and metabolics profiles in driving mental and physical ill-health. These approaches include mixed-effects modelling as this is suited to data where samples are observed repeatedly, Bayesian modelling as this can be used to estimate

the level of uncertainity in our parameter estimations [45, 46], structural equation modelling [47], and more data-driven techniques [48-50] such as hierarchical cluster analysis [15, 24, 51], latent profile analysis [52], and group-based trajectory modelling [53] will be applied. To take advantage of the multidimensional and longitudinal nature of the data collected, machine learning approaches can be used to build models predictive, at baseline, of downstream physical and mental ill-health outcomes. Algorithms that also provide some transparency in variable importance such as tree-based algorithms (Random Forest, XGBoost) and penalised regression (LASSO, Elastic-net) will be suitable for this.

To handle missing data points, we will also use (i) maximum likelihood approaches as these can estimate the most likely value of a parameter based on the observed data points, and (ii) multiple imputation to generate multiple imputed datasets where each dataset is analysed separately and the results are pooled. This approach ascertains the sensitivity of the statistical analysis based on different imputation estimates.

ETHICS AND DISSEMINATION

This study protocol was approved by the University of Sydney (HREC USYD 2015/867) and St Vincent's Hospital Human Research Ethics Committees (HREC SVH 17/045). Following confirmation that potential participants from the Uspace inpatient cohort are of mental and intellectual capacity to give informed consent, and have no language barriers, a complete description of the study will be discussed and eligible participants will be given a Participant Information Sheet and Consent Form and followed-up by the researcher for informed written consent, no less than 24 hours later, with those under the age of 18 having their parent or guardian also consent. This study is minimally invasive, and any adverse outcomes will inform procedure.

All participant data will be de-identified and stored in accordance with applicable security standards; therefore, the privacy of all participants will be protected.

The research findings will be disseminated through publications in peer-reviewed journals and conference proceedings, and participant data will be non-identifiable.

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CONTRIBUTORS

IBH and EMS conceived the research idea, designed the study, and are the principal investigators (for corresponding sites); AMT contributed to study conception, wrote the study protocol with input of JSC (actigraphy), AG (hormonal and metabolic measurements), KH, LP, and EMS. AMT manages the study with input of EMS, KH, and LP. EMS contributes to clinical organization; KH and LP manage patient unit participation and supervision. AMT wrote the first draft of the manuscript; CR, AG and YJCS contributed to major edits in later versions. All authors contributed to discussion and have approved the final protocol manuscript.

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COMPETING INTERESTS

Professor Ian Hickie was an inaugural Commissioner on Australia's National Mental Health Commission (2012-18). He is the Co-Director, Health and Policy at the Brain and Mind Centre (BMC) University of Sydney. The BMC operates an early-intervention youth services at Camperdown under contract to headspace. Professor Hickie has previously led community-based and pharmaceutical industry-supported (Wyeth, Eli Lily, Servier, Pfizer, AstraZeneca) projects focused on the identification and better management of anxiety and depression. He was a member of the Medical Advisory Panel for Medibank Private until October 2017, a Board Member of Psychosis Australia Trust and a member of Veterans Mental Health Clinical Reference group. He is the Chief Scientific Advisor to, and a 5% equity shareholder in, InnoWell Pty Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the $30 M Australian Government-funded Project Synergy

(2017-20; a three-year program for the transformation of mental health services) and to lead transformation of mental health services internationally through the use of innovative technologies.

A/Prof Elizabeth Scott is the Medical Director, Young Adult Mental Health Unit, St Vincent's Hospital Darlinghurst, Discipline Leader of Adult Mental Health, School of Medicine, University of Notre Dame, Research Affiliate, The University of Sydney and Consultant Psychiatrist. She has received honoraria for educational seminars related to the clinical management of depressive disorders supported by Servier and Eli-Lilly pharmaceuticals. She has participated in a national advisory board for the antidepressant compound Pristiq, manufactured by Pfizer. She was the National Coordinator of an antidepressant trial sponsored by Servier.