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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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3 **Protocol for a Young Adult Mental Health (Uspace) Cohort: Personalising**
4 **multidimensional care in young people admitted to hospital.**
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8 Ashleigh M Tickell^{a,b*}, Cathrin Rohleder^a, Alexandra H Garland^a, Yun Ju Christine Song^a,
9 Joanne S Carpenter^a, Kate Harel^b, Lisa Parker^b, Ian B Hickie^a Elizabeth M Scott^b,
10
11
12
13

14 ^aClinical Research Unit, Brain and Mind Centre, University of Sydney, Australia.
15

16 ^b Young Adult Mental Health Unit, Uspace, St Vincent's Private Hospital, Australia
17
18
19
20
21

22 Corresponding author:
23

24 Ashleigh M Tickell,
25

26 100 Mallett Street, Camperdown, NSW 2050
27

28 ashleigh.tickell@sydney.edu.au
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30 02 9114 4204
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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-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 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 clinical, 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

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

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6 The “Personalised Multidimensional Care” study focuses on an inpatient young adult mental
7 health clinic (Uspace). A key strength of this cohort is in its heterogeneity and ability to capture
8 a presently severe hospitalised sample of young adults with varying mental disorders. The
9 cohort will allow for studying a wide range of personalised interventions, whilst also examining
10 the longitudinal trajectory of this young, more severely ill cohort, and the associations between
11 detailed clinical, hormonal and metabolic profiles, social, neurocognitive, functional and
12 circadian outcomes.
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19 As previously demonstrated, the use of Health Information Technologies (HITs)
20 (computerised, self-reported e-health technologies such as the InnoWell Platform (Project
21 Synergy, InnoWell Pty Ltd) [19]) facilitates systematic multidimensional assessment in young
22 people seeking help [20], enables opportune and timely responses from service providers and
23 clinicians [20], and will, therefore, facilitate the development and delivery of highly
24 personalised and measurement-based treatment plans.
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30 The multidimensional assessments (clinical, functional, cognitive, circadian, metabolic, and
31 hormonal) and resulting personalised interventions will enhance knowledge and inform clinical
32 practice to improve standard clinical care in an inpatient unit. However, personalised care
33 means implementation of new protocols, training, and practice, as well as cultivating a new
34 conceptual framework [21, 22]. This study will integrate these approaches to help further
35 knowledge in the field and facilitate translational changes to mental health care. Importantly,
36 the personalised care approach based on multidimensional assessments is a collaborative
37 approach and requires multidisciplinary teams of health professionals and involves shared
38 decision-making based on the participant’s best interests [22, 23].
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48 **METHODS AND ANALYSIS**

49 **Study design and setting**

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51 This prospective, transdiagnostic, observational study will offer recruitment to all inpatients
52 aged 16-30 admitted to the Young Adult Mental Health Unit (Uspace), St Vincent’s Private
53 Hospital Sydney, Australia. Uspace is a voluntary private mental health service, targeted to the
54 needs of young adults. Furthermore, it is a unique multidisciplinary clinical setting for research.
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3 Patients are referred for the assessment of mental health problems; with a mission to promote
4 recovery and psychological well-being of young adults with severe and emerging mental health
5 problems.
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9 This “Personalised Multidimensional Care” study will be conducted over a period of 5 years,
10 from early 2020, with assessments at baseline and possible longitudinal follow-up available
11 upon participant consent up to 24 months. The selection of participants as well as the
12 assessments are consistent with the transdiagnostic ‘Research Domain Criteria’ (RDoC)
13 approach [24] as a means of classifying mental disorders based on neurobiological and
14 behavioural (in this case, functional, circadian, hormonal, metabolic, and cognitive) measures.
15 Furthermore, this study utilizes a subject sample (i.e. across the inpatient unit) with the
16 appropriate variance as advocated by proponents of the RDoC approach [25].
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25 **Participant and public involvement**

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

40 Study participants are currently admitted young adult inpatients, aged 16-30, presenting with a
41 severe affective episode (i.e. depressive, manic, anxious; including those with psychotic
42 features).
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45 Exclusion criteria for this study are: (i) insufficient fluency in the English language to
46 participate in the cognitive testing; (ii) inability to consent due to intellectual impairment (for
47 example, IQ < 70 as determined by the treating psychiatrist/psychologist) or severity of mental
48 illness (as determined by the treating psychiatrist/psychologist); and (iii) refusal to provide
49 informed consent.
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54 Comorbid or pre-existing childhood-onset conditions (for example Attention Deficit
55 Hyperactivity Disorder (ADHD) and conduct disorder), as well as alcohol or other substance
56 misuse or autistic spectrum disorders are not exclusion criteria.
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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 device, 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

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

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

21 Known childhood-onset disorders (i.e. with clear onset prior to 12 years old) are recorded in
22 addition to current diagnoses.
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27 *Family History of Mental Illness*

28 Known family history of mental illness in first degree relatives is recorded.
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33 *Treatment Utilisation/History*

34 Exposure to classes of medication (antidepressant, antipsychotic, mood stabiliser, or stimulant
35 medication), and hospitalisation overnight or longer due to a mental health problem (including
36 specification of hospitalisation due to illness severity or suicidality) are recorded.
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41 *Alcohol and Substance Use*

42 The presence of any reported use of tobacco, alcohol, cannabis, stimulants, or other drugs is
43 recorded.
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48 *Clinical Symptoms*

49 Initial questions obtain key demographic and clinical information, focusing on critical illness
50 course variables (for example, onset of symptoms, hospitalizations, age of first help seeking).
51 Standardised questionnaires include the 10-item Kessler Psychological Distress Scale (K-10)
52 [26] to detect psychological distress, with scores ranging between 10 and 50 (a score over 30
53 representing a likely severe mental disorder); Quick Inventory of Depressive Symptomatology
54 (QIDS-16) [27] to assess severity of depressive symptoms, with scores ranging between 1 and
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3 27 (a higher score representing greater severity of depression); Overall Anxiety Severity and
4 Impairment Scale (OASIS), a 5-item measure for assessment of severity and impairment in
5 regard to anxiety symptoms [28], with scores ranging between 0 and 20 (a higher score
6 representing a higher frequency and severity of anxiety (across anxiety disorders); Psychosis
7 Screener derived from Community Assessment of Psychic Experiences (CAPE)[29], a positive
8 symptoms scale and psychosis screener, developed to measure the lifetime prevalence of
9 psychotic-like experiences in the general population; Hypomania Screener derived from the
10 Altman Self-Rating Mania Scale (ASRM) [30], a 5-item self-rating scale to assess the severity
11 of manic symptoms, a higher score (five or more) indicating a high probability of a manic or
12 hypomanic condition; Suicidal Ideation Attributes Scale (SIDAS) [31], a 5-item scale to screen
13 participants for suicidal thoughts and severity of these thoughts, with scores ranging between
14 0 and 50 (a higher score representing more severe suicidal thoughts (a score over 21 being in
15 the high risk category); and, the Somatic and Psychological Health Report (SPHERE-12) [32],
16 a 12-item measure to screen for current depression and/or anxiety-like symptoms (a score of
17 two or more on the psychological subscale and a score of three or more on the somatic subscale
18 indicating current depression and/or anxiety-like symptoms).

31 32 33 Neurocognitive Screening

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

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39 A trained research psychologist or psychiatric registrar at Uspace will administer the cognitive
40 testing battery, which includes computerized assessments. First, premorbid intellectual
41 functioning ('predicted IQ') is estimated on the basis of performance on the Wechsler Test of
42 Adult Reading[33]. Following this, participants complete tests from the Cambridge
43 Neuropsychological Test Automated Battery (CANTAB)[34] on an HIT platform. CANTAB
44 tests have the advantage of being largely non-verbal (i.e. language-independent, culture-free)
45 and have been described in detail elsewhere [34-36]. Five tasks are included in this study: the
46 Motor Screening Task (MOT), an introductory task to prepare participants for testing (i.e. not
47 included in overall results) using induction of sensorimotor and comprehension; the Verbal
48 Recognition Memory task (VRM immediate and recall/delayed) assessing 'verbal memory and
49 new learning' indexed by the encoding and subsequent retrieval of verbal information scores;
50 the Attention Switching Task (AST) assessing 'mental flexibility' and indexed by the total
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3 adjusted score; the Paired Association Learning task (PAL) assessing 'visuo-spatial learning
4 and memory' indexed by the total adjusted errors score from; and, the Rapid Visual Processing
5 task (RVP) assessing 'sustained attention' and indexed by the RVP A prime (sensitivity to the
6 target).
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10 Participants' individual, normed results are calculated by a trained research psychologist within
11 two to three days of completion of cognitive testing battery. Calculation of CANTAB z-scores
12 are completed for each participant. While each participant's predicted IQ is assessed in the
13 cognitive screener, this is specifically to personalize results based on each participant's age,
14 education and background, compared to 'demographically corrected' standardised scores (z-
15 scores) using an internal normative database of healthy controls (<http://www.camocog.com>).
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20 21 Sleep-Wake Cycle/Circadian Profile 22

23 Participants are given an actigraphy watch (GENEActiv watch, Activinsights Ltd., Kimbolton,
24 UK) to wear on the non-dominant wrist during the admission period for a maximum of 14 days
25 and a minimum of 6 days. This actigraph records motor activity levels, skin temperature, and
26 ambient light exposure continuously at a rate of 30hz for the duration of the recording period.
27 The GENEActiv devices have been validated against several types of accelerometry-based
28 activity monitors[37-39] as well as for sleep-wake scoring [40]. More specifically, sleep-wake
29 detection in data collected with the GENEActiv devices has been found to have strong
30 reliability and validity when compared to data collected with other GENEActiv monitors or
31 with Actiwatch Spectrum devices (a well-established instrument in sleep and circadian
32 research) [40]. For over three decades, actigraphy monitors like the GENEActiv devices have
33 been considered as non-invasive instruments to measure sleep and activity patterns and have
34 been used extensively for research purposes in diverse clinical settings including: sleep
35 disorders, various medical illnesses (e.g. cancer, HIV, traumatic brain injuries,
36 neurodegenerative diseases) and mental disorders (e.g. anxiety, depression, bipolar and
37 psychotic disorders).
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50 Metabolic and hormonal profiles 51

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

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11 Once both the self-report questionnaire and cognitive testing have been completed by the
12 participant, and the clinical assessment form has been completed by the admitting clinician, a
13 feedback report will be generated (within 7 days of the completed assessments). A brief
14 feedback session will be organised with the participant in order to go through and explain
15 results and what that means in terms of more personalised intervention. This feedback report
16 and session will be between the participant, treating clinician and clinical researcher. The
17 feedback session will be part of the standard clinical care whereby the results of the testing will
18 be explained in detail to the participant, management options will be explored, and any
19 questions the participant may have will be addressed; furthermore, briefing will occur during
20 the participant's weekly clinical reviews. The feedback session aims to give the participant a
21 better understanding of certain aspects of their mental health and wellbeing and what they, and
22 their clinicians, can do to improve those areas. A feedback report of the actigraphy (sleep-wake
23 cycle and circadian) assessment results will be provided to the clinician upon completion of
24 the total time (maximum 14 days) wearing the actigraphy watch.
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26 The results of the multidimensional assessments – including clinical, functional, cognitive,
27 circadian, metabolic, and hormonal profiles – as well as the feedback session will inform
28 personalised interventions offered to the young adult participant in a shared decision-making
29 process.
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36 **Sample size calculation**

37 We aim to have a sample size of 400, based on the number of inpatients admitted to Uspace
38 over this period.
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45 **Data analysis plan**

46 Once completed, the data from the self-report assessment is collated, and displays a detailed
47 and immediate dashboard of results. This information is available to a trained research
48 psychologist immediately upon the participant's completion of the self-report assessment and
49 will be used to prepare the feedback report.
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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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4 *young people attending early intervention mental health services in Australia: a*
5 *longitudinal study*. BMJ open, 2018. **8**(3): p. e020678.
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10 **CONTRIBUTORS**

11 IBH and EMS conceived the research idea, designed the study, and are the principal
12 investigators (for corresponding sites); AMT contributed to study conception, wrote the study
13 protocol with input of JSC (actigraphy), AG (hormonal and metabolic measurements), KH, LP,
14 and EMS. AMT manages the study with input of EMS, KH, and LP. EMS contributes to
15 clinical organization; KH and LP manage patient unit participation and supervision. AMT
16 wrote the first draft of the manuscript; CR, AG and YJCS contributed to major edits in later
17 versions. All authors contributed to discussion and have approved the final protocol
18 manuscript.
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29 to the Young Adult Mental Health Unit, St Vincent's Private Hospital.
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34 **COMPETING INTERESTS**

35 Professor Ian Hickie was an inaugural Commissioner on Australia's National Mental Health
36 Commission (2012-18). He is the Co-Director, Health and Policy at the Brain and Mind Centre
37 (BMC) University of Sydney. The BMC operates an early-intervention youth services at
38 Camperdown under contract to headspace. Professor Hickie has previously led community-
39 based and pharmaceutical industry-supported (Wyeth, Eli Lilly, Servier, Pfizer, AstraZeneca)
40 projects focused on the identification and better management of anxiety and depression. He
41 was a member of the Medical Advisory Panel for Medibank Private until October 2017, a
42 Board Member of Psychosis Australia Trust and a member of Veterans Mental Health Clinical
43 Reference group. He is the Chief Scientific Advisor to, and a 5% equity shareholder in,
44 InnoWell Pty Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC
45 (Australia; 45% equity) to deliver the \$30 M Australian Government-funded Project Synergy
46 (2017-20; a three-year program for the transformation of mental health services) and to lead
47 transformation of mental health services internationally through the use of innovative
48 technologies.
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3 A/Prof Elizabeth Scott is the Medical Director, Young Adult Mental Health Unit, St Vincent's
4 Hospital Darlinghurst, Discipline Leader of Adult Mental Health, School of Medicine,
5 University of Notre Dame, Research Affiliate, The University of Sydney and Consultant
6 Psychiatrist. She has received honoraria for educational seminars related to the clinical
7 management of depressive disorders supported by Servier and Eli-Lilly pharmaceuticals. She
8 has participated in a national advisory board for the antidepressant compound Pristiq,
9 manufactured by Pfizer. She was the National Coordinator of an antidepressant trial sponsored
10 by Servier.
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BMJ Open

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

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3 **Protocol for a Young Adult Mental Health (Uspace) Cohort: Personalising**
4 **multidimensional care in young people admitted to hospital.**
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8 Ashleigh M Tickell^{a,b*}, Cathrin Rohleder^a, Alexandra H Garland^a, Yun Ju Christine Song^a,
9 Joanne S Carpenter^a, Kate Harel^b, Lisa Parker^b, Ian B Hickie^a Elizabeth M Scott^b,
10
11
12
13

14 ^aClinical Research Unit, Brain and Mind Centre, University of Sydney, Australia.
15

16 ^b Young Adult Mental Health Unit, Uspace, St Vincent's Private Hospital, Australia
17
18
19
20
21

22 Corresponding author:
23

24 Ashleigh M Tickell,
25

26 100 Mallett Street, Camperdown, NSW 2050
27

28 ashleigh.tickell@sydney.edu.au
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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

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3 means implementation of new protocols, training, and practice, as well as cultivating a new
4 conceptual framework [24, 25]. We have previously shown that it is feasible to integrate
5 technology and neurocognitive testing as standard clinical care in an inpatient unit, and that
6 neurocognitive profiling may help us to better understand the illness severity in young patients
7 [24]. Based on these results, we have decided to add further routine assessments (e.g.,
8 circadian, metabolic, and hormonal profiling) to be able to routinely provide personalised and
9 measurement-based care. This study will integrate these approaches to help further knowledge
10 in the field and facilitate translational changes to mental health care. Importantly, the
11 personalised care approach based on multidimensional assessments is a collaborative approach
12 and requires multidisciplinary teams of health professionals and involves shared decision-
13 making based on the participant's best interests [25, 26].
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25 **METHODS AND ANALYSIS**

26 **Study design and setting**

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30 This prospective, transdiagnostic, observational study will offer recruitment to all inpatients
31 aged 16-30 admitted to the Young Adult Mental Health Unit (Uspace), St Vincent's Private
32 Hospital Sydney, Australia. Uspace is a voluntary private mental health service, targeted to the
33 needs of young adults. Furthermore, it is a unique multidisciplinary clinical setting for research.
34 Patients are referred for the assessment of mental health problems; with a mission to promote
35 recovery and psychological well-being of young adults with severe and emerging mental health
36 problems.
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43 This "Personalised Multidimensional Care" study has started in March 2020 and will be
44 conducted over a period of 5 years with assessments at baseline and possible longitudinal
45 follow-up available upon participant consent up to 24 months. That is, with the patient's
46 consent we will invite patients back for a follow-up study. At 24 months the assessments
47 conducted at baseline will be repeated. This will inform a unique tracking of the patients from
48 a inpatient facility. We are in the process of an ethics amendment to include an additional 6
49 month and 12 month follow-up to improve the care provided as we have found this to be
50 effective in previous experience with other studies.
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56 The recruitment will be based on the presentation to care and is not restricted by specific
57 diagnostic criteria. The diagnosis-independent selection of participants as well as the
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3 comprehensive assessments are consistent with the transdiagnostic ‘Research Domain Criteria’
4 (RDoC) approach [27]. RDoC aims to classify mental disorders based on neurobiological and
5 behavioural measures that cut across current disorder categories. The use of functional,
6 circadian, hormonal, metabolic, and cognitive assessments, allows to attain a comprehensive
7 picture of the individuals admitted to USpace, and a subsequent classification based on
8 biobehavioral dimensions. Furthermore, as this study is offered young people admitted to
9 USpace independent from diagnosis (i.e., we will not exclude young people with a primary
10 diagnosis outside a target category, a co-morbid disorder or those who have some, but not all
11 of the criteria required for a diagnosis of a specific disorder), our resulting cohort will have the
12 appropriate variance as advocated by proponents of the RDoC approach [28]. However, the
13 vast majority of young people admitted to USpace will have a primary diagnosis of an affective
14 disorder. These include depressive disorder, anxiety disorder, bipolar disorder, or affective
15 psychosis.
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28 **Participant and public involvement**

29 The Health Information Technology (HIT) system (InnoWell Platform (InnoWell Pty Ltd)
30 [22], which will be used for the collection of self-report data in the study, has been developed
31 with participant and public involvement. Although young people were consulted during the
32 development of the technology used to measure relevant outcomes of the study, they were not
33 invited to comment on the study design. However, we will invite patient and public
34 involvement representatives to help us writing a plain language summary of the results and
35 developing our dissemination strategy.
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43 **Patient Cohort**

44 Study participants are currently admitted young adult inpatients, aged 16-30, presenting with a
45 severe affective episode (i.e. depressive, manic, anxious; including those with psychotic
46 features). Diagnosis will be a consensus diagnosis; that is, via multidisciplinary clinical
47 assessment (by psychiatrists, psychologists and allied health professionals).
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50 Exclusion criteria for this study are: (i) insufficient fluency in the English language to
51 participate in the cognitive testing; (ii) inability to consent due to intellectual impairment (for
52 example, IQ < 70 as determined by the treating psychiatrist/psychologist) or severity of mental
53 illness (as determined by the treating psychiatrist/psychologist); and (iii) refusal to provide
54 informed consent.
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3 Comorbid or pre-existing childhood-onset conditions (for example Attention Deficit
4 Hyperactivity Disorder (ADHD) and conduct disorder), as well as alcohol or other substance
5 misuse or autistic spectrum disorders are not exclusion criteria.
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10 **Study course and procedures**

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

50 An overview and timeline of the assessments is provided in Table 1.
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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
<i>Routine assessments</i>												
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	
Feedback Session (Actigraphy)			X			X			X			X
<i>Additional assessments</i>												
Self report questionnaire (45 to 60 min)		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

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3 The presence of any reported use of tobacco, alcohol, cannabis, stimulants, or other drugs is
4 recorded.
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8 *Clinical Symptoms*

10 Initial questions obtain key demographic and clinical information, focusing on critical illness
11 course variables (for example, onset of symptoms, hospitalizations, age of first help seeking).
12 Standardised questionnaires include the 10-item Kessler Psychological Distress Scale (K-10)
13 [29] to detect psychological distress, with scores ranging between 10 and 50 (a score over 30
14 representing a likely severe mental disorder); Quick Inventory of Depressive Symptomatology
15 (QIDS-16) [30] to assess severity of depressive symptoms, with scores ranging between 1 and
16 27 (a higher score representing greater severity of depression); Overall Anxiety Severity and
17 Impairment Scale (OASIS), a 5-item measure for assessment of severity and impairment in
18 regard to anxiety symptoms [31], with scores ranging between 0 and 20 (a higher score
19 representing a higher frequency and severity of anxiety (across anxiety disorders); Psychosis
20 Screener derived from Community Assessment of Psychic Experiences (CAPE)[32], a positive
21 symptoms scale and psychosis screener, developed to measure the lifetime prevalence of
22 psychotic-like experiences in the general population; Hypomania Screener derived from the
23 Altman Self-Rating Mania Scale (ASRM) [33], a 5-item self-rating scale to assess the severity
24 of manic symptoms, a higher score (five or more) indicating a high probability of a manic or
25 hypomanic condition; Suicidal Ideation Attributes Scale (SIDAS) [34], a 5-item scale to screen
26 participants for suicidal thoughts and severity of these thoughts, with scores ranging between
27 0 and 50 (a higher score representing more severe suicidal thoughts (a score over 21 being in
28 the high risk category); and, the Somatic and Psychological Health Report (SPHERE-12) [35],
29 a 12-item measure to screen for current depression and/or anxiety-like symptoms (a score of
30 two or more on the psychological subscale and a score of three or more on the somatic subscale
31 indicating current depression and/or anxiety-like symptoms).
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51 Neurocognitive Screening

52 Self-reported, non-structured, standardised questions in regard to the participant's own sense
53 of cognition will be assessed prior to testing (for example, changes in everyday thinking skills
54 and neurocognitive abilities).
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3 A trained research psychologist or psychiatric registrar at Uspace will administer the cognitive
4 testing battery, which includes computerized assessments. First, premorbid intellectual
5 functioning ('predicted IQ') is estimated on the basis of performance on the Wechsler Test of
6 Adult Reading[36]. Following this, participants complete tests from the Cambridge
7 Neuropsychological Test Automated Battery (CANTAB)[37] on an HIT platform. CANTAB
8 tests have the advantage of being largely non-verbal (i.e. language-independent, culture-free)
9 and have been described in detail elsewhere [37-39]. Five tasks are included in this study: the
10 Motor Screening Task (MOT), an introductory task to prepare participants for testing (i.e. not
11 included in overall results) using induction of sensorimotor and comprehension; the Verbal
12 Recognition Memory task (VRM immediate and recall/delayed) assessing 'verbal memory and
13 new learning' indexed by the encoding and subsequent retrieval of verbal information scores;
14 the Attention Switching Task (AST) assessing 'mental flexibility' and indexed by the total
15 adjusted score; the Paired Association Learning task (PAL) assessing 'visuo-spatial learning
16 and memory' indexed by the total adjusted errors score from; and, the Rapid Visual Processing
17 task (RVP) assessing 'sustained attention' and indexed by the RVP A prime (sensitivity to the
18 target).

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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

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

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

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32 Once both the self-report questionnaire and cognitive testing have been completed by the
33 participant, and the clinical assessment form has been completed by the admitting clinician, a
34 feedback report will be generated (within 7 days of the completed assessments). A brief
35 feedback session will be organised with the participant in order to go through and explain
36 results and what that means in terms of more personalised intervention. This feedback report
37 and session will be between the participant, treating clinician and clinical researcher. The
38 feedback session will be part of the standard clinical care whereby the results of the testing will
39 be explained in detail to the participant, management options will be explored, and any
40 questions the participant may have will be addressed; furthermore, briefing will occur during
41 the participant's weekly clinical reviews. The feedback session aims to give the participant a
42 better understanding of certain aspects of their mental health and wellbeing and what they, and
43 their clinicians, can do to improve those areas. A feedback report of the actigraphy (sleep-wake
44 cycle and circadian) assessment results will be provided to the clinician upon completion of
45 the total time (maximum 14 days) wearing the actigraphy watch.
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56 The results of the multidimensional assessments – including clinical, functional, cognitive,
57 circadian, metabolic, and hormonal profiles – as well as the feedback session will inform
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3 personalised interventions offered to the young adult participant in a shared decision-making
4 process.
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8 **Sample size calculation**

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10 We aim to include 400 participants annually, based on our knowledge typically 700-800
11 inpatients are admitted to Uspace per year. Thus, we expect to be able to collect data from
12 2,000 participants over the period of the study. Although patient retention in youth mental
13 health services is difficult to predict [44], in our experience, 70% of inpatients are retained
14 from baseline and throughout follow-up assessments. This has been accounted for in our
15 sample size estimation.
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24 **Data analysis plan**

25 Once completed, the data from the self-report assessment is collated, and displays a detailed
26 and immediate dashboard of results. This information is available to a trained research
27 psychologist immediately upon the participant's completion of the self-report assessment and
28 will be used to prepare the feedback report.
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32 This "Personalised Multidimensional Care" study allows for the assessment of
33 multidimensional – i.e. clinical, functional, cognitive, circadian, metabolic, and hormonal –
34 profiles for young adult participants. This includes:
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- 37 • Evaluating parameters affecting participant outcomes such as cognitive impairments,
38 disturbed sleep-wake behaviours and circadian rhythms, clinical symptoms, and
39 functional impairments.
- 40 • Investigating associations between metabolic, hormonal, clinical, self-report, and
41 circadian factors.
- 42 • Comparisons with similar data from young people presenting to outpatient youth
43 mental health services (e.g. Brain and Mind Centre cohorts [9, 11-13]).
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50 As the data collected will be highly multidimensional, aside from the use of standard statistical
51 approaches (e.g. ANOVA, correlations, regression), we will employ more advanced statistical
52 techniques to investigate the underlying interactions between demographics, clinical
53 presentation, neurocognition, sleep-wake profiles, and metabolics profiles in driving mental
54 and physical ill-health. These approaches include mixed-effects modelling as this is suited to
55 data where samples are observed repeatedly, Bayesian modelling as this can be used to estimate
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3 the level of uncertainty in our parameter estimations [45, 46], structural equation modelling
4 [47], and more data-driven techniques [48-50] such as hierarchical cluster analysis [15, 24, 51],
5 latent profile analysis [52], and group-based trajectory modelling [53] will be applied. To take
6 advantage of the multidimensional and longitudinal nature of the data collected, machine
7 learning approaches can be used to build models predictive, at baseline, of downstream
8 physical and mental ill-health outcomes. Algorithms that also provide some transparency in
9 variable importance such as tree-based algorithms (Random Forest, XGBoost) and penalised
10 regression (LASSO, Elastic-net) will be suitable for this.

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

27 28 **ETHICS AND DISSEMINATION**

29
30 This study protocol was approved by the University of Sydney (HREC USYD 2015/867) and
31 St Vincent's Hospital Human Research Ethics Committees (HREC SVH 17/045). Following
32 confirmation that potential participants from the Uspace inpatient cohort are of mental and
33 intellectual capacity to give informed consent, and have no language barriers, a complete
34 description of the study will be discussed and eligible participants will be given a Participant
35 Information Sheet and Consent Form and followed-up by the researcher for informed written
36 consent, no less than 24 hours later, with those under the age of 18 having their parent or
37 guardian also consent. This study is minimally invasive, and any adverse outcomes will inform
38 procedure.

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

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

43 44 **References**

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58 *based care model to manage youth mental health - Personalising care options in youth*
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17 **CONTRIBUTORS**

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

34 This study received philanthropic funding support (scholarship) donated by the Cottle Family
35 to the Young Adult Mental Health Unit, St Vincent's Private Hospital.
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40 **COMPETING INTERESTS**

41 Professor Ian Hickie was an inaugural Commissioner on Australia's National Mental Health
42 Commission (2012-18). He is the Co-Director, Health and Policy at the Brain and Mind Centre
43 (BMC) University of Sydney. The BMC operates an early-intervention youth services at
44 Camperdown under contract to headspace. Professor Hickie has previously led community-
45 based and pharmaceutical industry-supported (Wyeth, Eli Lilly, Servier, Pfizer, AstraZeneca)
46 projects focused on the identification and better management of anxiety and depression. He
47 was a member of the Medical Advisory Panel for Medibank Private until October 2017, a
48 Board Member of Psychosis Australia Trust and a member of Veterans Mental Health Clinical
49 Reference group. He is the Chief Scientific Advisor to, and a 5% equity shareholder in,
50 InnoWell Pty Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC
51 (Australia; 45% equity) to deliver the \$30 M Australian Government-funded Project Synergy
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3 (2017-20; a three-year program for the transformation of mental health services) and to lead
4 transformation of mental health services internationally through the use of innovative
5 technologies.
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8 A/Prof Elizabeth Scott is the Medical Director, Young Adult Mental Health Unit, St Vincent's
9 Hospital Darlinghurst, Discipline Leader of Adult Mental Health, School of Medicine,
10 University of Notre Dame, Research Affiliate, The University of Sydney and Consultant
11 Psychiatrist. She has received honoraria for educational seminars related to the clinical
12 management of depressive disorders supported by Servier and Eli-Lilly pharmaceuticals. She
13 has participated in a national advisory board for the antidepressant compound Pristiq,
14 manufactured by Pfizer. She was the National Coordinator of an antidepressant trial sponsored
15 by Servier.
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BMJ Open

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

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Complete List of Authors:	Tickell, Ashleigh; The University of Sydney, Brain and Mind Centre Rohleder, Cathrin; The University of Sydney, Brain and Mind Centre Garland, Alexandra; The University of Sydney, Brain and Mind Centre Song, Yun; The University of Sydney, Brain and Mind Centre Carpenter, Joanne; University of Sydney Brain and Mind Research Institute, ; Harel, Kate; St Vincent's Private Hospital, Young Adult Mental Health Unit Parker, Lisa; St Vincent's Private Hospital, Young Adult Mental Health Unit Hickie, Ian; The University of Sydney, Brain and Mind Centre; Scott, Elizabeth; St Vincent's Private Hospital, Young Adult Mental Health Unit
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3 **Protocol for a Young Adult Mental Health (Uspace) Cohort: Personalising**
4 **multidimensional care in young people admitted to hospital.**
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8 Ashleigh M Tickell^{a,b*}, Cathrin Rohleder^a, Alexandra H Garland^a, Yun Ju Christine Song^a,
9 Joanne S Carpenter^a, Kate Harel^b, Lisa Parker^b, Ian B Hickie^a Elizabeth M Scott^b,
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13

14 ^aClinical Research Unit, Brain and Mind Centre, University of Sydney, Australia.
15

16 ^b Young Adult Mental Health Unit, Uspace, St Vincent's Private Hospital, Australia
17
18
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21

22 Corresponding author:
23

24 Ashleigh M Tickell,
25

26 100 Mallett Street, Camperdown, NSW 2050
27

28 ashleigh.tickell@sydney.edu.au
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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

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3 means implementation of new protocols, training, and practice, as well as cultivating a new
4 conceptual framework [24, 25]. We have previously shown that it is feasible to integrate
5 technology and neurocognitive testing as standard clinical care in an inpatient unit, and that
6 neurocognitive profiling may help us to better understand the illness severity in young patients
7 [24]. Based on these results, we have decided to add further routine assessments (e.g.,
8 circadian, metabolic, and hormonal profiling) to be able to routinely provide personalised and
9 measurement-based care. This study will integrate these approaches to help further knowledge
10 in the field and facilitate translational changes to mental health care. Importantly, the
11 personalised care approach based on multidimensional assessments is a collaborative approach
12 and requires multidisciplinary teams of health professionals and involves shared decision-
13 making based on the participant's best interests [25, 26].
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25 **METHODS AND ANALYSIS**

26 **Study design and setting**

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30 This prospective, transdiagnostic, observational study will offer recruitment to all inpatients
31 aged 16-30 admitted to the Young Adult Mental Health Unit (Uspace), St Vincent's Private
32 Hospital Sydney, Australia. Uspace is a voluntary private mental health service, targeted to the
33 needs of young adults. Furthermore, it is a unique multidisciplinary clinical setting for research.
34 Patients are referred for the assessment of mental health problems; with a mission to promote
35 recovery and psychological well-being of young adults with severe and emerging mental health
36 problems.
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43 This "Personalised Multidimensional Care" study has started in March 2020 and will be
44 conducted over a period of 5 years with assessments at baseline and possible longitudinal
45 follow-up available upon participant consent up to 24 months (estimated end date of
46 recruitment: March 2023; estimated date of study completion: March 2025). That is, with the
47 patient's consent, we will invite patients back for a follow-up assessment. At 24 months the
48 assessments conducted at baseline will be repeated. This will inform a unique tracking of the
49 patients from an inpatient facility. We are in the process of an ethics amendment to include an
50 additional 6 month and 12 month follow-up to improve the care provided as we have found
51 this to be effective in previous experience with other studies.
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3 The recruitment will be based on the presentation to care and is not restricted by specific
4 diagnostic criteria. The diagnosis-independent selection of participants as well as the
5 comprehensive assessments are consistent with the transdiagnostic ‘Research Domain Criteria’
6 (RDoC) approach [27]. RDoC aims to classify mental disorders based on neurobiological and
7 behavioural measures that cut across current disorder categories. The use of functional,
8 circadian, hormonal, metabolic, and cognitive assessments, allows to attain a comprehensive
9 picture of the individuals admitted to USpace, and a subsequent classification based on
10 biobehavioral dimensions. Furthermore, as this study is offered young people admitted to
11 USpace independent from diagnosis (i.e., we will not exclude young people with a primary
12 diagnosis outside a target category, a co-morbid disorder or those who have some, but not all
13 of the criteria required for a diagnosis of a specific disorder), our resulting cohort will have the
14 appropriate variance as advocated by proponents of the RDoC approach [28]. However, the
15 vast majority of young people admitted to USpace will have a primary diagnosis of an affective
16 disorder. These include depressive disorder, anxiety disorder, bipolar disorder, or affective
17 psychosis.

31 **Participant and public involvement**

32 The Health Information Technology (HIT) system (InnoWell Platform (InnoWell Pty Ltd)
33 [22], which will be used for the collection of self-report data in the study, has been developed
34 with participant and public involvement. Although young people were consulted during the
35 development of the technology used to measure relevant outcomes of the study, they were not
36 invited to comment on the study design. However, we will invite patient and public
37 involvement representatives to help us writing a plain language summary of the results and
38 developing our dissemination strategy.

46 **Patient Cohort**

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

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

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6 Comorbid or pre-existing childhood-onset conditions (for example Attention Deficit
7 Hyperactivity Disorder (ADHD) and conduct disorder), as well as alcohol or other substance
8 misuse or autistic spectrum disorders are not exclusion criteria.
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11 12 13 **Study course and procedures**

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15 Potential participants who are admitted to USpace and interested in participating will be
16 referred to the research study at arms-length to ensure that there is minimal perceived coercion
17 from the referring clinician to the participant to participate in the study. The participant will
18 then be in-depth informed by the research staff based in the clinic to introduce the study and
19 undertake consent. Through consecutive referral, eligible participants who are newly admitted
20 to USpace will be booked in to complete neurocognitive testing and self-report questionnaires
21 after informed written consent. Participants' availability and booking schedule is based around
22 their own routine appointments and groups as inpatients, with most participants being booked
23 within four days of admission. Hormonal and metabolic measures are routinely collected at
24 USpace on admission as part of standard clinical care, this data will also be used for research
25 purposes on and during admission as indicated by standard of care, regardless of entry into the
26 study. Neurocognitive testing (CANTAB) is completed on a tablet device, taking between 40
27 and 50 minutes. The self-report questionnaire will be completed the day after neurocognitive
28 testing, taking approximately 45 to 60 minutes. Both, neurocognitive testing and the self-report
29 questionnaire can be split and completed on two consecutive days. Actigraphy watches will be
30 set up to record and given to patients to wear once informed consent is provided. Participants
31 will wear the actigraphy watches during the admission period for a maximum of 14 days and a
32 minimum of 6 days. No supervision is needed during wearing of the actiwatches. The
33 appropriate clinician that admitted the corresponding participant during the admission process
34 will complete a 'Clinical Assessment Form'. The multidimensional assessments as well as the
35 feedback session will inform personalised interventions offered to the young adult participants
36 in a shared decision-making process.
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53 At follow-up, all assessments are repeated except for clinical assessment, as we expect that the
54 follow-up assessments will be conducted after discharge in almost all cases,. Therefore, the
55 clinical assessment is only done in participants re-admitted to USpace within the follow-up
56 period.
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60 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
<i>Standard routine assessments</i>												
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	
Feedback Session (Actigraphy)			X			X			X			X
<i>Additional assessments</i>												
Self report questionnaire (45 to 60 min)		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

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3 The presence of any reported use of tobacco, alcohol, cannabis, stimulants, or other drugs is
4 recorded.
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8 *Clinical Symptoms*

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10 Initial questions obtain key demographic and clinical information, focusing on critical illness
11 course variables (for example, onset of symptoms, hospitalizations, age of first help seeking).
12 Standardised questionnaires include the 10-item Kessler Psychological Distress Scale (K-10)
13 [29] to detect psychological distress, with scores ranging between 10 and 50 (a score over 30
14 representing a likely severe mental disorder); Quick Inventory of Depressive Symptomatology
15 (QIDS-16) [30] to assess severity of depressive symptoms, with scores ranging between 1 and
16 27 (a higher score representing greater severity of depression); Overall Anxiety Severity and
17 Impairment Scale (OASIS), a 5-item measure for assessment of severity and impairment in
18 regard to anxiety symptoms [31], with scores ranging between 0 and 20 (a higher score
19 representing a higher frequency and severity of anxiety (across anxiety disorders); Psychosis
20 Screener derived from Community Assessment of Psychic Experiences (CAPE)[32], a positive
21 symptoms scale and psychosis screener, developed to measure the lifetime prevalence of
22 psychotic-like experiences in the general population; Hypomania Screener derived from the
23 Altman Self-Rating Mania Scale (ASRM) [33], a 5-item self-rating scale to assess the severity
24 of manic symptoms, a higher score (five or more) indicating a high probability of a manic or
25 hypomanic condition; Suicidal Ideation Attributes Scale (SIDAS) [34], a 5-item scale to screen
26 participants for suicidal thoughts and severity of these thoughts, with scores ranging between
27 0 and 50 (a higher score representing more severe suicidal thoughts (a score over 21 being in
28 the high risk category); and, the Somatic and Psychological Health Report (SPHERE-12) [35],
29 a 12-item measure to screen for current depression and/or anxiety-like symptoms (a score of
30 two or more on the psychological subscale and a score of three or more on the somatic subscale
31 indicating current depression and/or anxiety-like symptoms).
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51 Neurocognitive Screening

52 Self-reported, non-structured, standardised questions in regard to the participant's own sense
53 of cognition will be assessed prior to testing (for example, changes in everyday thinking skills
54 and neurocognitive abilities).
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3 A trained research psychologist or psychiatric registrar at Uspace will administer the cognitive
4 testing battery, which includes computerized assessments. First, premorbid intellectual
5 functioning ('predicted IQ') is estimated on the basis of performance on the Wechsler Test of
6 Adult Reading[36]. Following this, participants complete tests from the Cambridge
7 Neuropsychological Test Automated Battery (CANTAB)[37] on an HIT platform. CANTAB
8 tests have the advantage of being largely non-verbal (i.e. language-independent, culture-free)
9 and have been described in detail elsewhere [37-39]. Five tasks are included in this study: the
10 Motor Screening Task (MOT), an introductory task to prepare participants for testing (i.e. not
11 included in overall results) using induction of sensorimotor and comprehension; the Verbal
12 Recognition Memory task (VRM immediate and recall/delayed) assessing 'verbal memory and
13 new learning' indexed by the encoding and subsequent retrieval of verbal information scores;
14 the Attention Switching Task (AST) assessing 'mental flexibility' and indexed by the total
15 adjusted score; the Paired Association Learning task (PAL) assessing 'visuo-spatial learning
16 and memory' indexed by the total adjusted errors score from; and, the Rapid Visual Processing
17 task (RVP) assessing 'sustained attention' and indexed by the RVP A prime (sensitivity to the
18 target).

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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

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

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

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32 Once both the self-report questionnaire and cognitive testing have been completed by the
33 participant, and the clinical assessment form has been completed by the admitting clinician, a
34 feedback report will be generated (within 7 days of the completed assessments). A brief
35 feedback session will be organised with the participant in order to go through and explain
36 results and what that means in terms of more personalised intervention. This feedback report
37 and session will be between the participant, treating clinician and clinical researcher. The
38 feedback session will be part of the standard clinical care whereby the results of the testing will
39 be explained in detail to the participant, management options will be explored, and any
40 questions the participant may have will be addressed; furthermore, briefing will occur during
41 the participant's weekly clinical reviews. The feedback session aims to give the participant a
42 better understanding of certain aspects of their mental health and wellbeing and what they, and
43 their clinicians, can do to improve those areas. A feedback report of the actigraphy (sleep-wake
44 cycle and circadian) assessment results will be provided to the clinician upon completion of
45 the total time (maximum 14 days) wearing the actigraphy watch.
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56 The results of the multidimensional assessments – including clinical, functional, cognitive,
57 circadian, metabolic, and hormonal profiles – as well as the feedback session will inform
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3 personalised interventions offered to the young adult participant in a shared decision-making
4 process.
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8 **Sample size calculation**

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10 We aim to include 400 participants annually, based on our knowledge typically 700-800
11 inpatients are admitted to Uspace per year. Thus, we expect to be able to collect data from
12 2,000 participants over the period of the study. Although patient retention in youth mental
13 health services is difficult to predict [44], in our experience, 70% of inpatients are retained
14 from baseline and throughout follow-up assessments. This has been accounted for in our
15 sample size estimation.
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24 **Data analysis plan**

25 Once the participants have completed the self-report assessment, the data is collated and
26 displayed as a detailed and immediate dashboard of results. This information is available to a
27 trained research psychologist immediately upon the participant's completion of the self-report
28 assessment and will be used to prepare the feedback report.
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32 This "Personalised Multidimensional Care" study allows for the assessment of
33 multidimensional – i.e. clinical, functional, cognitive, circadian, metabolic, and hormonal –
34 profiles for young adult participants. This includes:
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- 37 • Evaluating parameters affecting participant outcomes such as cognitive impairments,
38 disturbed sleep-wake behaviours and circadian rhythms, clinical symptoms, and
39 functional impairments.
- 40 • Investigating associations between metabolic, hormonal, clinical, self-report, and
41 circadian factors.
- 42 • Comparisons with similar data from young people presenting to outpatient youth
43 mental health services (e.g. Brain and Mind Centre cohorts [9, 11-13]).
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50 As the data collected will be highly multidimensional, aside from the use of standard statistical
51 approaches (e.g. ANOVA, correlations, regression), we will employ more advanced statistical
52 techniques to investigate the underlying interactions between demographics, clinical
53 presentation, neurocognition, sleep-wake profiles, and metabolics profiles in driving mental
54 and physical ill-health. These approaches include mixed-effects modelling as this is suited to
55 data where samples are observed repeatedly, Bayesian modelling as this can be used to estimate
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3 the level of uncertainty in our parameter estimations [45, 46], structural equation modelling
4 [47], and more data-driven techniques [48-50] such as hierarchical cluster analysis [15, 24, 51],
5 latent profile analysis [52], and group-based trajectory modelling [53] will be applied. To take
6 advantage of the multidimensional and longitudinal nature of the data collected, machine
7 learning approaches can be used to build models predictive, at baseline, of downstream
8 physical and mental ill-health outcomes. Algorithms that also provide some transparency in
9 variable importance such as tree-based algorithms (Random Forest, XGBoost) and penalised
10 regression (LASSO, Elastic-net) will be suitable for this.

11
12 To handle missing data points, we will also use (i) maximum likelihood approaches as these
13 can estimate the most likely value of a parameter based on the observed data points, and (ii)
14 multiple imputation to generate multiple imputed datasets where each dataset is analysed
15 separately and the results are pooled. This approach ascertains the sensitivity of the statistical
16 analysis based on different imputation estimates.

27 28 **ETHICS AND DISSEMINATION**

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

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

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

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17 **CONTRIBUTORS**

18 IBH and EMS conceived the research idea, designed the study, and are the principal
19 investigators (for corresponding sites); AMT contributed to study conception, wrote the study
20 protocol with input of JSC (actigraphy), AG (hormonal and metabolic measurements), KH, LP,
21 and EMS. AMT manages the study with input of EMS, KH, and LP. EMS contributes to
22 clinical organization; KH and LP manage patient unit participation and supervision. AMT
23 wrote the first draft of the manuscript; CR, AG and YJCS contributed to major edits in later
24 versions. All authors contributed to discussion and have approved the final protocol
25 manuscript.
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35 to the Young Adult Mental Health Unit, St Vincent's Private Hospital.
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40 **COMPETING INTERESTS**

41 Professor Ian Hickie was an inaugural Commissioner on Australia's National Mental Health
42 Commission (2012-18). He is the Co-Director, Health and Policy at the Brain and Mind Centre
43 (BMC) University of Sydney. The BMC operates an early-intervention youth services at
44 Camperdown under contract to headspace. Professor Hickie has previously led community-
45 based and pharmaceutical industry-supported (Wyeth, Eli Lilly, Servier, Pfizer, AstraZeneca)
46 projects focused on the identification and better management of anxiety and depression. He
47 was a member of the Medical Advisory Panel for Medibank Private until October 2017, a
48 Board Member of Psychosis Australia Trust and a member of Veterans Mental Health Clinical
49 Reference group. He is the Chief Scientific Advisor to, and a 5% equity shareholder in,
50 InnoWell Pty Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC
51 (Australia; 45% equity) to deliver the \$30 M Australian Government-funded Project Synergy
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3 (2017-20; a three-year program for the transformation of mental health services) and to lead
4 transformation of mental health services internationally through the use of innovative
5 technologies.
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8 A/Prof Elizabeth Scott is the Medical Director, Young Adult Mental Health Unit, St Vincent's
9 Hospital Darlinghurst, Discipline Leader of Adult Mental Health, School of Medicine,
10 University of Notre Dame, Research Affiliate, The University of Sydney and Consultant
11 Psychiatrist. She has received honoraria for educational seminars related to the clinical
12 management of depressive disorders supported by Servier and Eli-Lilly pharmaceuticals. She
13 has participated in a national advisory board for the antidepressant compound Pristiq,
14 manufactured by Pfizer. She was the National Coordinator of an antidepressant trial sponsored
15 by Servier.
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