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Youth Mental Health Tracker: Protocol to establish a longitudinal cohort and research database for young people attending Australian mental health services.

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Youth Mental Health Tracker: Protocol to establish a longitudinal cohort and research database for young people attending Australian mental health services.

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Abstract

Introduction Mental disorders are a leading cause of long-term disability worldwide. Much of the burden of mental ill health is mediated by early onset, comorbidities with physical health conditions, and chronicity of the illnesses. This study aims to track the early period of mental disorders amongst young people presenting to Australian mental health services to facilitate: more streamlined transdiagnostic processes; highly personalised and measurement-based care; secondary prevention; and enhanced long-term outcomes.

Methods and analysis Recruitment to this large-scale, multi-site, prospective, transdiagnostic, longitudinal clinical cohort study (*'Youth Mental Health Tracker'*) will be offered to all young people between the ages of 12 and 30 years presenting to participating services with proficiency in English and no history of intellectual disability. Young people will be tracked over three years with standardised assessments at baseline and three, six, 12, 24, and 36 months. Assessments will include self-report and clinician-administered measures, covering five key domains including: (1) social and occupational function; (2) self-harm, suicidal thoughts and behaviour; (3) alcohol or other substance misuse; (4) physical health; and (5) illness type, clinical stage and trajectory. Data collection will be facilitated by the use of a health information technology. The data will be used to: (1) determine prospectively the course of multi-dimensional functional outcomes, based on the differential impact of demographics, medication, psychological interventions, and other key potentially modifiable moderator variables; and (2) map pathophysiological mechanisms and clinical illness trajectories to determine transition rates of young people to more severe illness forms.

Ethics and dissemination The study has been reviewed and approved by the Human Research Ethics Committee of the Sydney Local Health District (SLHD, 2019/ETH00469). All data will be

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non-identifiable and research findings will be disseminated through peer-reviewed journals and scientific conference presentations.

Article Summary

Strengths and limitations of this study:

- This study focusses on presentation care, rather than diagnosis-based, recruitment to establish a comprehensive and transdiagnostic longitudinal cohort and research database of young people attending Australian mental health services.
- Our aim is to track up to 5,000 young people (aged between 12 and 30 years) over a three-year period.
- The use of our multi-dimensional outcomes framework enables comprehensive assessment of young people as well as routine monitoring.
- The study does not yet include standardised objective measures such as biomarker, data on brain structure and function, and neuropsychological assessments.
- The study is part of a clinical trials framework evaluating the utility of our multidimensional outcomes framework as well as our pathophysiological mechanism and illness trajectory model.

Introduction

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Mental disorders are a leading cause of premature death and persistent disability worldwide.[1-4] In those aged 10 to 24 years, neuropsychiatric disorders contribute more than any other cause to the global burden of disease.[5] In addition to the early age of onset of mental disorders, factors including their prevalence, chronicity, comorbidity with physical illness, risky alcohol or other substance use, and high suicide risk and self-harm behaviour significantly contribute to significant disability and premature mortality.[6-15] Consequently, earlier identification, personalised early interventions, secondary prevention, and enhanced long-term care in the early phases of these disorders are key priorities to reduce persistent disability and premature mortality.[16-18]

In order to better characterise the individual needs and enable highly personalised and measurement-based care, we have proposed the use of a multi-dimensional outcomes framework.[15, 19-21] This framework comprises five key domains, namely:

- social and occupational function;
- self-harm, suicidal thoughts and behaviours;
- alcohol or other substance misuse;
- physical health; and
- illness type, clinical stage, and trajectory.

These domains can be assessed by using various freely accessible validated scales and standardised questionnaires[20]. New health information technologies (HIT), such as the InnoWell Platform (Project Synergy, InnoWell Pty Ltd)[22], can facilitate the delivery of such comprehensive assessments, as they allow clinicians to implement time-efficient self-report

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versions of the scales and questionnaires that can often be completed by consumers without guidance.[20]

The assessment and identification of individual needs in each domain may prove to be particularly valuable, as it allows clinicians to develop highly personalised care options targeting specific factors associated with illness persistence and more significant disability across disorders (e.g. functional impairment, physical illnesses, risky alcohol or other substance use, and high suicide risk and self-harm behaviour). [19, 23]

Young people presenting to mental health services commonly experience a variety of symptoms that are often less specific (e.g. anxiety, high level of psychological distress, sleep problems, mood instability, variable psychosocial function) and not yet sufficiently severe to meet thresholds for assigning specific diagnostic categories. Thus, current syndrome-focused classification systems, and their matching clinical guidelines, often map poorly onto the earlier phases of mental illness. [18, 24-28] A transdiagnostic clinical staging model has been proposed as an adjunct to formal diagnosis in order to address this problem. The clinical staging model reflects the progression of mental disorders and is based on the staging concept used in general medicine, wherein more advanced stages are associated with a poorer prognosis and a need for more intensive interventions with a higher risk-to-benefit ratio.[18, 29] General medicine also shows that an understanding of underlying pathophysiological mechanisms is crucial for selecting optimal treatment. Identifying mood and psychotic syndromes (including anxiety, depression, bipolar disorder, psychosis) based on pathophysiology will allow clinicians to select treatment options targeting underlying causes and, thus, eventually lead to improved clinical outcomes.[30]

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We have proposed three underlying pathophysiological mechanisms (neurodevelopmental abnormalities, hyperarousal, circadian dysfunction), which over time influence individual illness trajectories to three different illness types, namely psychosis, anxious depression, and bipolar spectrum disorders, respectively.[18, 31] Importantly, there is a degree of overlap between the three pathways at all stages of illness. Previously, we have shown in a similar cohort study that 27% of young people with emerging mental disorders progress across stages and between pathways throughout care. This included 13% progressing between pathways whilst developing more specific and severe symptoms.[18] Continuous tracking of long-term outcomes will provide detailed information on these individual trajectories and factors influencing them, and, most importantly, will allow for early identification of changing needs that require adjustments of individual interventions. Furthermore, the information on clinical illness trajectories of young people can be used to determine transition rates to more severe illness forms (e.g. severe depression, bipolar or psychotic disorder) and may help to better understand which factors drive the progression of illness.

Objectives of the study and conceptual framework

Mental disorders emerge early in life and evolve dynamically over time. The longitudinal *'Youth Mental Health Tracker'* study aims to better understand the complex and variable clinical course (trajectories and pathophysiological mechanisms) of mental disorders and their impacts over time by tracking long-term multidimensional outcomes in a youth mental health cohort.

Standardised multi-dimensional clinical information will be routinely and confidentially collected across participating services. The study involves multiple longitudinal assessments so that key illness outcomes (i.e., social and occupational function, self-harm, suicidal thoughts and behaviour, alcohol or other substance misuse, physical health; and illness type,

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clinical stage, and trajectory) can be measured and tracked over time. Importantly, this allows for the detection of treatment non-responders at an early stage of illness; that is, before extensive exposure to interventions and chronic manifestation of illness.

In summary, such standardised data collection will enable improved identification, characterisation and profiling of mental disorders in young people; thus, enabling the identification of new targets and mechanisms that can be translated into more streamlined transdiagnostic processes, the development of the next generation of highly personalised interventions, and health service strategies that greatly enhance care for young people.

Methods and analysis

Study design and setting

This is a large-scale, multi-site, prospective, transdiagnostic, longitudinal clinical cohort study (*Youth Mental Health Tracker*), with the Brain and Mind Centre (including *headspace* Camperdown, and Early Intervention and High Intensity Services; public health organisation) at the University of Sydney (Sydney, Australia), being the lead site for this study. Further, St Vincent's Private Hospital (USpace) (private health organisation) will be another participating site in Sydney, Australia. Thus, this study involves specialist and enhanced primary-care based youth mental health services.

For the collection and storage of routine clinical data across sites, a HIT system will facilitate the data extraction and use in a de-identified manner for research purposes.

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The study is expected to start in late 2019. Participants will be tracked over three years with standardised assessments occurring at baseline and three, six, 12, 24, and 36 months.

Patient and public involvement

The health information technology (HIT) system (InnoWell Platform (InnoWell Pty Ltd)[22] that will be used by sites participating in the study for self-report assessments was developed with patient and public involvement and has been approved as medical device by the Australian Register of Therapeutic Goods (ARTG ID: 315030).[32]

Study Population

This study focusses on young people seeking treatment for emergent mood and psychotic syndromes and aims to establish a comprehensive transdiagnostic, longitudinal clinical cohort. Therefore, the recruitment is based on presentation for care, and is not restricted by specific diagnostic criteria. This diagnosis-independent recruitment is consistent with the National Institute of Mental Health recommendations to conduct more inclusive clinical research in cohorts drawn from similar standard service settings,[33] and facilitate translation of the findings to other youth mental health care settings.

Inclusion and exclusion criteria

Participation in this study will be offered to all young people between the ages of 12 and 30 years, presenting to participating youth mental health service sites. Young people who do not have proficiency in the English language or have an intellectual disability (at investigator's

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discretion) will be excluded due to inability to accurately complete study scales and questionnaires.

Recruitment procedure

All young people presenting to participating youth mental health services and meet inclusion and exclusion and exclusion criteria, will be invited to participate in this Youth Mental Health Tracker study.

Study course and procedures

All participants recruited to this Youth Mental Health Tracker study will undergo a standardised baseline assessment (t_0, details see below), which will be conducted by a health professional at the service. Standard information on demographics, medical history, and physical history will be collected, and a range of clinician-administered assessments will be conducted. The young person will also complete a suite of online self-report questionnaires.

Participants that complete the baseline assessment will be followed up and invited to complete an online assessment that will consist of the self-report questionnaire pack (completed online at home). These follow up assessments will be done at three and six months following the baseline assessment (t_3, t_6).

To ensure optimal participant care is maintained, all participants will be invited to attend the service they initially presented to, for annual clinical routine assessments (t_{12}, t_{24}, t_{36}). Clinician administered assessments and self-report questionnaires will be repeated to track individual

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outcomes. That is, young people will be tracked on at least an annual basis over 36 months (Figure 1).

Assessments

In order to provide improved characterisation and profiling of the Australian youth mental health population, multi-dimensional self-report and clinician-administered measures (outlined below) will be deployed. These cover the five key domains of the multi-dimensional assessment and outcomes framework.[15, 20]

The self-report questionnaires (see Table 1) collect information regarding social and occupational function, self-harm, suicidal thoughts and behaviours (STB), alcohol or other substance misuse, physical health as well as lifetime and current psychiatric symptoms, family history of mental illness, and medical history. The questionnaires will be hosted online by using the InnoWell Platform (InnoWell Pty Ltd).[22]

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Table 1: Overview of self-report questionnaires.

Health Domain	Psychometric tool
Distress	• Kessler Psychological Distress Scale (K10)[34, 35]
Suicidal thoughts & behaviour	• The Suicidal Ideation Attributes Scale (SIDAS)[36] • The Columbia–Suicide Severity Rating Scale (C-SSRS)[37]
Psychosis-like experiences	• Prodromal Questionnaire (PQ-16)[38]
Mania-like experiences	• Altman Self-Rating Mania Scale (ASRM)[39]
Daily activities	• Youth not in education or employment (NEET), Organisation for Economic Co-operation and Development (OECD) • Census of Population and Housing, Australian Bureau of Statistics (ABS) • WHO Disability Assessment Schedule (WHODAS 2.0)[40] - 'unable to carry out usual activities' question • Work and Social Adjustment Scale (WSAS)[41] • Social and Occupational Functioning Assessment Scale (SOFAS)[42]-adapted for self-report
Self-harm	• Brief Non-suicidal Self-Injury Assessment Tool (B-NSSI-AT)[43]
Tobacco	• The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)[44, 45]
Alcohol	• The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) [44, 45] • AUDIT alcohol consumption questions (AUDIT-C)[46]
Relationships	• 'Perceived social support' and 'conflict in close relationships' were measured by an adapted version of the Schuster's Social Support Scale (SSSS)[47]
Depression	• Quick Inventory of Depressive Symptomatology - self-report (QIDS-SR)[48]
Anxiety	• Overall anxiety severity and impairment scale (OASIS)[49]
Physical health	• Height, weight, and waist circumference • International physical activity questionnaire (IPAQ)[50, 51]
Sleep-wake cycle	• Sleep timing items are based on the Pittsburgh Sleep Quality Index (PSQI)[52], and Munich ChronoType Questionnaire (MCTQ)[53, 54] • Sleep quality items are based on expert consensus in the literature
Post-traumatic stress	• Primary Care PTSD Screen for DSM-5 (PC-PTSD-5)[55]
Eating behaviours and body image	• Modelled on the Eating Disorder Examination (EDE)[56]. Derived from structured interview questions from the Health Omnibus Surveys
Cannabis	• The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) [44, 45]

As part of the clinical routine assessments[20], clinicians will record additional information regarding functioning, clinical stages, common illness subtypes, and possible underlying pathophysiological mechanisms. More precisely this includes:

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(1) *Social and Occupational Assessment Scale (SOFAS*) reflecting the clinician's judgment of overall social and occupational function;

(2) *Clinical Global Improvement (CGI),* providing an overall clinician-rated summary measure that takes information on the patient's history, psychosocial circumstances, symptoms, behaviour, and the impact of the symptoms in the patient's ability to function into account;

(3) *common illness subtypes* (psychosis, anxious depression, bipolar spectrum) *and possible underlying pathophysiological mechanisms* (neurodevelopmental, hyperarousal, circadian)[18, 31], and;

(4) *Clinical Staging.*[18, 25, 29, 57] Based on the clinical staging assessment[18, 25, 29, 57], participants will be distinguished as those in the earliest phases with non-specific clinical presentations (stages 1a 'seeking help') from those at greater-risk with more specific, sub-threshold presentations (stage 1b) or experiencing first major illness episodes (stages 2+).

Following the continuation of this Youth Mental Health Tracker study, this may further include neuropsychological and neurobiological (genetic, metabolic, circadian, and imaging) assessments in a subset of participants as required by their clinicians based on need, to reflect an approach that is patient-centred care and highly personalised.

Sample size calculation

The clinics that are participating in the project provide early intervention mental health services along with assistance in promoting young peoples' wellbeing. As such, there is no set sample size for the establishment of this cohort. Based on previous recruitment numbers of past research studies in these settings, the annual number of young people enrolled in the study is expected to be a minimum of 1000. This number will sufficiently detect even the

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smallest effect sizes to investigate prospectively, over three years, the course of multi-dimensional functional outcomes (social and occupational function; self-harm, suicidal thoughts and behaviours; alcohol or other substance misuse; physical health)[15, 19] in young people presenting to youth-specific mental health services.

Data analysis plan

This Youth Mental Health Tracker study will allow us to determine prospectively, over three years, the course of key multi-dimensional functional and clinical outcomes, in young people presenting to youth mental health services. This includes:

1. Modelling the impacts of demographic, treatment and other key potentially modifiable moderator variables, on functional and clinical outcomes;
2. Mapping the clinical illness trajectories and pathophysiological mechanisms of young people to determine transition rates to more severe illness forms (e.g., severe depression, bipolar or psychotic disorder);
3. Investigating the differential effects of duration of exposure to antipsychotic, antidepressant, or mood-stabilising medications on physical health, clinical outcomes, and risks to self-harm or suicidal behaviour.

We will make use of high-level statistical techniques including mixed-effects/ multilevel modelling, Bayesian modelling[58-60], structural equation modelling[61], and data-driven techniques[62-64] such as hierarchical cluster analysis[65-67], latent profile analysis[68], and group-based trajectory modelling.[69]

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Ethics and dissemination

The study has been reviewed and approved by the Human Research Ethics Committee (HREC) of the Sydney Local Health District (SLHD, 2019/ETH00469, protocol version v1-2, 01/07/2019). Protocol modifications will only be implemented after HREC approval.

This is a research database study, therefore, consent process is entirely concerned with permissions regarding the storage and use of routinely collected data. For this reason, an opt-out consent process has been implemented. Potential participants presenting to the service at the participating sites will be in-depth informed by the clinicians about the study. The opt-out consent will be conducted at an *'arm's length approach'*. Participants will have sufficient time to consider whether they would like to participate in the research project. Young people under the age of 15 will initially undergo the standard consent process. However, the young participants who do not opt-out of the study will be required to obtain additional parent/guardian consent. Participants can withdraw from the study at any time. Participants will be assured that their decision to participate will not affect their treatment, nor the current or future relationship with their treating clinician or researchers at the service. All participant data will be de-identified and stored in accordance with applicable security standards; therefore, the privacy of all participants will be protected. Research findings will be disseminated through peer-reviewed journals and scientific conference presentations, and participant data will be non-identifiable.

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Contributors

IBH conceived the research idea, designed the study, and is the principal investigator. CR and YJCS contributed to study conception and wrote the study protocol with input of IBH, JJC, TAD, FI, BH, NZ, AN, JSC, AMT, CW, SPC, AJG, DK, FML, EMS. CR wrote the manuscript with input of IBH, YJCS, JJC, TAD, FI, BH, NZ, AN, JSC, and AMT. All authors critically reviewed content and approved the final version of the publication.

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Competing interests

Project Synergy (2014–2016) was commissioned by the Department of Health and conducted by the Young and Well Cooperative Research Centre (Young and Well CRC) in partnership with the University of Sydney's Brain and Mind Centre. The Department of Health (Australian Government) has further supported Project Synergy through a significant investment over 3 years (2017–2020) which led to the development of InnoWell Pty Ltd, a joint venture between the University of Sydney and PricewaterhouseCoopers (Australia) (PwC). The University of Sydney and PwC (Australia) each have a 45% shareholding in InnoWell. The remaining 10% shareholding is evenly shared between Professor Jane Burns and Professor Ian Hickie.

Legends

Figure 1: Overview of study visits. After completing the baseline visit, participants will be followed-up once yearly. During each visit, self-report questionnaires and clinical routine assessments have to be completed. In addition, participants will be asked to complete self-report questionnaires also 3 and 6 months after study start.

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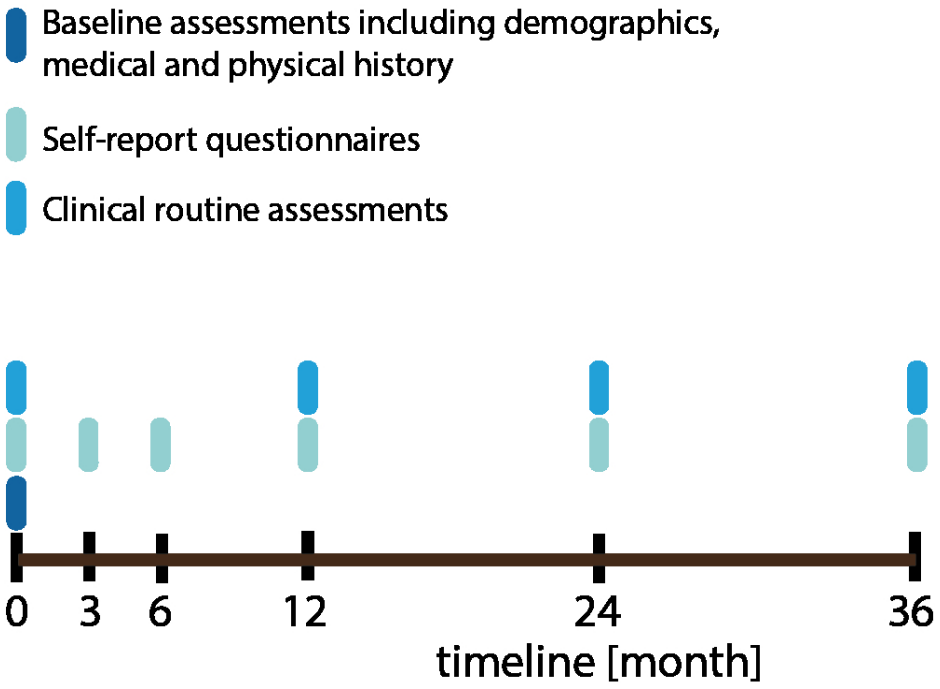

Overview of study visits. / After completing the baseline visit, participants will be followed-up once yearly. During each visit, self-report questionnaires and clinical routine assessments have to be completed. In addition, participants will be asked to complete self-report questionnaires also 3 and 6 months after study start.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on page #
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	NA
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	14
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	6-7

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Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	NA
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1, 8-12
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			**NA**

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Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13

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	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA
Methods: Monitoring			**NA**
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA

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Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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BMJ Open

Youth Mental Health Tracker: Protocol to establish a longitudinal cohort and research database for young people attending Australian mental health services.

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Youth Mental Health Tracker: Protocol to establish a longitudinal cohort and research database for young people attending Australian mental health services.

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Abstract

Introduction Mental disorders are a leading cause of long-term disability worldwide. Much of the burden of mental ill health is mediated by early onset, comorbidities with physical health conditions, and chronicity of the illnesses. This study aims to track the early period of mental disorders amongst young people presenting to Australian mental health services to facilitate: more streamlined transdiagnostic processes; highly personalised and measurement-based care; secondary prevention; and enhanced long-term outcomes.

Methods and analysis Recruitment to this large-scale, multi-site, prospective, transdiagnostic, longitudinal clinical cohort study (*'Youth Mental Health Tracker'*) will be offered to all young people between the ages of 12 and 30 years presenting to participating services with proficiency in English and no history of intellectual disability. Young people will be tracked over three years with standardised assessments at baseline and three, six, 12, 24, and 36 months. Assessments will include self-report and clinician-administered measures, covering five key domains including: (1) social and occupational function; (2) self-harm, suicidal thoughts and behaviour; (3) alcohol or other substance misuse; (4) physical health; and (5) illness type, clinical stage and trajectory. Data collection will be facilitated by the use of a health information technology. The data will be used to: (1) determine prospectively the course of multi-dimensional functional outcomes, based on the differential impact of demographics, medication, psychological interventions, and other key potentially modifiable moderator variables; and (2) map pathophysiological mechanisms and clinical illness trajectories to determine transition rates of young people to more severe illness forms.

Ethics and dissemination The study has been reviewed and approved by the Human Research Ethics Committee of the Sydney Local Health District (SLHD, 2019/ETH00469). All data will be

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non-identifiable, and research findings will be disseminated through peer-reviewed journals and scientific conference presentations.

Article Summary

Strengths and limitations of this study:

- This study focusses on presentation care, rather than diagnosis-based, recruitment to establish a comprehensive and transdiagnostic longitudinal cohort and research database of young people attending Australian mental health services.
- We aim to track up to 5,000 young people (aged between 12 and 30 years) over a three-year period.
- The use of our multi-dimensional outcomes framework enables comprehensive assessment of young people as well as routine monitoring.
- The study does not yet include standardised objective measures such as biomarkers, data on brain structure and function, and neuropsychological assessments.
- The study is part of a clinical trials framework evaluating the utility of our multidimensional outcomes framework as well as our pathophysiological mechanism and illness trajectory model.

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Introduction

Mental disorders are a leading cause of premature death and persistent disability worldwide.[1-4] In those aged 10 to 24 years, neuropsychiatric disorders contribute more than any other cause to the global burden of disease.[5] In addition to the early age of onset of mental disorders, factors including their prevalence, chronicity, comorbidity with physical illness, risky alcohol or other substance use, and high suicide risk and self-harm behaviour significantly contribute to significant disability and premature mortality.[6-15] Consequently, earlier identification, personalised early interventions, secondary prevention, and enhanced long-term care in the early phases of these disorders are key priorities to reduce persistent disability and premature mortality.[16-18]

In order to better characterise the individual needs and enable highly personalised and measurement-based care, we have proposed the use of a multi-dimensional outcomes framework.[15, 19-21] This framework comprises five key domains, namely:

- social and occupational function;
- self-harm, suicidal thoughts, and behaviours;
- alcohol or other substance misuse;
- physical health; and
- illness type, clinical stage, and trajectory.

These domains can be assessed by using various freely accessible validated scales and standardised questionnaires[20]. New health information technologies (HIT), such as the InnoWell Platform (Project Synergy, InnoWell Pty Ltd)[22], can facilitate the delivery of such comprehensive assessments, as they allow clinicians to implement time-efficient self-report

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versions of the scales and questionnaires that can often be completed by consumers without guidance.[20]

The assessment and identification of individual needs in each domain may prove to be particularly valuable, as it allows clinicians to develop highly personalised care options targeting specific factors associated with illness persistence and more significant disability across disorders (e.g. functional impairment, physical illnesses, risky alcohol or other substance use, and high suicide risk and self-harm behaviour). [19, 23]

Young people presenting to mental health services commonly experience a variety of symptoms that are often less specific (e.g. anxiety, high level of psychological distress, sleep problems, mood instability, variable psychosocial function) and not yet sufficiently severe to meet thresholds for assigning specific diagnostic categories. Thus, current syndrome-focused classification systems, and their matching clinical guidelines, often map poorly onto the earlier phases of mental illness. [18, 24-28] A transdiagnostic clinical staging model has been proposed as an adjunct to formal diagnosis in order to address this problem. The clinical staging model reflects the progression of mental disorders and is based on the staging concept used in general medicine, wherein more advanced stages are associated with a poorer prognosis and a need for more intensive interventions with a higher risk-to-benefit ratio.[18, 29]

A detailed description of the this transdiagnostic staging model is given in references [18, 29]. In brief, the staging model distinguishes five stages. Each stage is defined by a degree of functional impairment and persistence of symptoms. Importantly, clinical stages are not expected to coincide with traditional diagnostic categories. The stages cover early illness phases characterised by non-specific symptoms accompanied by mild to moderate functional

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impairment (stage 1a) or "attenuated syndromes" of severe mental disorders, with moderate to severe functional impairments (stage 1b), as well as full-threshold syndromes with clear and ongoing functional impairment (stage 2), and later stages including recurrent or persistent illnesses with marked worsening in social, educational or occupational function due to persistence or recurrence (stage 3) or severe, persistent and unremitting illnesses with clear evidence of marked functional deterioration (stage 4). The staging model takes also comorbidities into account. In stage 1b cases, syndromes may be mixed in terms of their symptoms or complicated by alcohol and other substance misuse. After transition to stage 2, the syndrome may remain mixed in terms of symptoms, and not necessarily matching a single or discrete DSM-style disorder, or primary discrete syndromes may co-occur. The significant comorbidity may also include alcohol or other substance misuse, abnormal eating behaviour or other relevant psychological syndromes.

General medicine also shows that an understanding of underlying pathophysiological mechanisms is crucial for selecting optimal treatment. Identifying mood and psychotic syndromes (including anxiety, depression, bipolar disorder, psychosis) based on pathophysiology will allow clinicians to select treatment options targeting underlying causes and, thus, eventually lead to improved clinical outcomes.[30]

Based on the results of a cross-sectional study[31], we have proposed three underlying pathophysiological mechanisms (neurodevelopmental abnormalities, hyperarousal, circadian dysfunction), which over time influence individual illness trajectories to three different illness types, namely psychosis, anxious depression, and bipolar spectrum disorders, respectively.[18, 31] More precisely, the "neurodevelopmental-psychosis illness type" is characterised by psychotic features and significant and persistent developmental difficulties, including

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cognitive impairments, learning difficulties, and autism spectrum disorder. This subtype is based on evidence linking neurodevelopmental abnormalities with increased risk of developing psychotic phenomena[32-34] and is in line with meta-structures proposed for the redevelopment of diagnostic classification systems.[35, 36] The "hyperarousal-anxious depression" illness subtype includes cases with childhood anxiety, heightened stress sensitivity, and adolescent depressive syndromes. Also, cases without clear evidence for a neurodevelopmental-psychosis or circadian-bipolar spectrum illness subtype, are allocated to this subtype. It is consistent with models of neural fear circuitry, prolonged stress responses, and glucocorticoid-dependent arousal in anxiety and unipolar mood disorders.[37-40] the "circadian-bipolar spectrum" illness subtype is derived from models linking mood disorders with circadian disturbances and dysregulated activation and energy, and is characterised by disrupted sleep-wake behaviours and circadian rhythms, delayed sleep-waking timing and an atypical or bipolar spectrum symptom profile.[41-44]

Current research projects at BMC are investigating the validity and potential implementation of this approach within mental health services.[45, 46]

Importantly, there is a degree of overlap between the three pathways at all stages of illness. Previously, we have shown in a similar cohort study that 27% of young people with emerging mental disorders progress across stages and between pathways throughout care. This included 13% progressing between pathways whilst developing more specific and severe symptoms.[18] Continuous tracking of long-term outcomes will provide detailed information on these individual trajectories and factors influencing them, and, most importantly, will allow for early identification of changing needs that require adjustments of individual interventions. Furthermore, the information on clinical illness trajectories of young people can be used to determine transition rates to more severe illness forms (e.g. severe depression, bipolar or

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psychotic disorder) and may help to better understand which factors drive the progression of illness.

Objectives of the study and conceptual framework

Mental disorders emerge early in life and evolve dynamically over time. The longitudinal *'Youth Mental Health Tracker'* study aims to better understand the complex and variable clinical course (trajectories and pathophysiological mechanisms) of mental disorders and their impacts over time by tracking long-term multidimensional outcomes in a youth mental health cohort.

Standardised multi-dimensional clinical information will be routinely and confidentially collected across participating services. The study involves multiple longitudinal assessments so that key illness outcomes (i.e., social and occupational function, self-harm, suicidal thoughts and behaviour, alcohol or other substance misuse, physical health, and illness type, clinical stage, and trajectory) can be measured and tracked over time. Importantly, this allows for the detection of treatment non-responders at an early stage of illness; that is, before extensive exposure to interventions and chronic manifestation of illness.

In summary, such standardised data collection will enable improved identification, characterisation and profiling of mental disorders in young people; thus, enabling the identification of new targets and mechanisms that can be translated into more streamlined transdiagnostic processes, the development of the next generation of highly personalised interventions, and health service strategies that greatly enhance care for young people.

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Methods and analysis

Study design and setting

This is a large-scale, multi-site, prospective, transdiagnostic, longitudinal clinical cohort study (*Youth Mental Health Tracker*), with the Brain and Mind Centre (including *headspace* Camperdown, and Early Intervention and High Intensity Services; public health organisation) at the University of Sydney (Sydney, Australia), being the lead site for this study. Further, St Vincent's Private Hospital (USpace) (private health organisation) will be another participating site in Sydney, Australia. Thus, this study involves both *specialist* (USpace) and *enhanced primary-care* (*headspace* Camperdown, and Early Intervention and High Intensity Services) youth mental health services.

For the collection and storage of routine clinical data across sites, a HIT system will facilitate the data extraction and use in a de-identified manner for research purposes.

The study is expected to start in late 2019. Participants will be tracked over three years with standardised assessments occurring at baseline and three, six, 12, 24, and 36 months.

Patient and public involvement

The health information technology (HIT) system (InnoWell Platform (InnoWell Pty Ltd)[22] that will be used by sites participating in the study for self-report assessments was developed with patient and public involvement and has been approved as medical device by the Australian Register of Therapeutic Goods (ARTG ID: 315030).[47] Although young people were consulted

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during the development of the technology used to measure relevant outcomes of the study, they were not invited to comment on the study design.

Study Population

This study focusses on young people seeking treatment for emergent mood and psychotic syndromes and aims to establish a comprehensive transdiagnostic, longitudinal clinical cohort. Therefore, the recruitment is based on presentation for care, and is not restricted by specific diagnostic criteria. That is, young people presenting with non-specific anxiety or depressive symptoms according to diagnostic criteria (stage 1a), attenuated syndromes (stage 1b) or full-threshold, major, and discrete syndromes (stage 2+) will be included.

This diagnosis-independent recruitment is consistent with the National Institute of Mental Health recommendations to conduct more inclusive clinical research in cohorts drawn from similar standard service settings,[48] and facilitate translation of the findings to other youth mental health care settings.

However, the vast majority who presents to the participating ambulatory-care clinical services have 'internalising' disorders (anxiety, depression, mood or psychotic disorders etc.), often associated with role impairment, comorbid substance misuse and suicidal thoughts and behaviours. The proportion of persons with major 'externalising' disorders as their primary difficulty is low.

Inclusion and exclusion criteria

Participation in this study will be offered to all young people, presenting to participating youth mental health service sites that provide mental health support to young people between the ages of 12 and 30 years. Young people who do not have proficiency in the English language or have an intellectual disability (at investigator's discretion, based on standard procedures at

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each site) will be excluded due to inability to accurately complete study scales and questionnaires.

Recruitment procedure

All young people presenting to participating youth mental health services and meet inclusion and exclusion and exclusion criteria, will be invited to participate in this Youth Mental Health Tracker study.

Study course and procedures

All participants recruited to this Youth Mental Health Tracker study will undergo a standardised baseline assessment (t_0, details see below), which will routinely be conducted by a mental health professional at the service. Standard information on demographics, medical history, and physical history will be collected, and a range of clinician-administered assessments will be conducted. The young person will also complete a suite of online self-report questionnaires.

Participants that complete the baseline assessment will be followed up and invited to complete an online assessment that will consist of the self-report questionnaire pack (completed online at home). These follow up assessments will be done at three and six months following the baseline assessment (t_3, t_6).

To ensure optimal participant care is maintained, all participants will be invited to attend the service they initially presented to, for annual clinical routine assessments (t_{12}, t_{24}, t_{36}). Clinician

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administered assessments and self-report questionnaires will be repeated to track individual outcomes. That is, young people will be tracked on at least an annual basis over 36 months (Figure 1).

Assessments

In order to provide improved characterisation and profiling of the Australian youth mental health population, multi-dimensional self-report and clinician-administered measures (outlined below) will be deployed. These cover the five key domains of the multi-dimensional assessment and outcomes framework.[20, 49]

The self-report questionnaires (see Table 1) collect information regarding social and occupational function, self-harm, suicidal thoughts and behaviours (STB), alcohol or other substance misuse, physical health as well as lifetime and current psychiatric symptoms, family history of mental illness, and medical history. The questionnaires will be hosted online by using the InnoWell Platform (InnoWell Pty Ltd).[22]

Table 1: Overview of self-report questionnaires.

Health Domain	Psychometric tool
Distress	• Kessler Psychological Distress Scale (K10)[50, 51]
Suicidal thoughts & behaviour	• The Suicidal Ideation Attributes Scale (SIDAS)[52] • The Columbia–Suicide Severity Rating Scale (C-SSRS)[53]
Psychosis-like experiences	• Prodromal Questionnaire (PQ-16)[54]
Mania-like experiences	• Altman Self-Rating Mania Scale (ASRM)[55]
Daily activities	• Youth not in education or employment (NEET), Organisation for Economic Co-operation and Development (OECD) • Census of Population and Housing, Australian Bureau of Statistics (ABS) • WHO Disability Assessment Schedule (WHODAS 2.0)[56] - 'unable to carry out usual activities' question

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	• Work and Social Adjustment Scale (WSAS)[57] • Social and Occupational Functioning Assessment Scale (SOFAS)[58]-adapted for self-report
Self-harm	• Brief Non-suicidal Self-Injury Assessment Tool (B-NSSI-AT)[59]
Tobacco	• The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)[60, 61]
Alcohol	• The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) [60, 61] • AUDIT alcohol consumption questions (AUDIT-C)[62]
Relationships	• 'Perceived social support' and 'conflict in close relationships' were measured by an adapted version of the Schuster's Social Support Scale (SSSS)[63]
Depression	• Quick Inventory of Depressive Symptomatology - self-report (QIDS-SR)[64]
Anxiety	• Overall anxiety severity and impairment scale (OASIS)[65]
Physical health	• Height, weight, and waist circumference • International physical activity questionnaire (IPAQ)[66, 67]
Sleep-wake cycle	• Sleep timing items are based on the Pittsburgh Sleep Quality Index (PSQI)[68], and Munich ChronoType Questionnaire (MCTQ)[69, 70] • Sleep quality items are based on expert consensus in the literature
Post-traumatic stress	• Primary Care PTSD Screen for DSM-5 (PC-PTSD-5)[71]
Eating behaviours and body image	• Modelled on the Eating Disorder Examination (EDE)[72]. Derived from structured interview questions from the Health Omnibus Surveys
Cannabis	• The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) [60, 61]

As part of the clinical routine assessments[20], clinicians will record additional information regarding functioning, clinical stages, common illness subtypes, and possible underlying pathophysiological mechanisms. More precisely this includes:

(1) *Social and Occupational Assessment Scale (SOFAS*) reflecting the clinician's judgment of overall social and occupational function;

(2) *Clinical Global Improvement (CGI),* providing an overall clinician-rated summary measure that takes information on the patient's history, psychosocial circumstances, symptoms, behaviour, and the impact of the symptoms in the patient's ability to function into account;

(3) *common illness subtypes* (psychosis, anxious depression, bipolar spectrum) *and possible underlying pathophysiological mechanisms* (neurodevelopmental, hyperarousal, circadian)[18,

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[31], and;

(4) *Clinical Staging.*[18, 25, 29, 73] Based on the clinical staging assessment[18, 25, 29, 73], participants will be distinguished as those in the earliest phases with non-specific clinical presentations (stages 1a 'seeking help') from those at greater-risk with more specific, sub-threshold presentations (stage 1b) or experiencing first major illness episodes (stages 2+).

Following the continuation of this Youth Mental Health Tracker study, this may further include neuropsychological and neurobiological (genetic, metabolic, circadian, and imaging) assessments in a subset of participants as required by their clinicians based on need, to reflect an approach that is patient-centred care and highly personalised.

Sample size calculation

The clinics that are participating in the project provide early intervention mental health services along with assistance in promoting young peoples' wellbeing. As such, there is no set sample size for the establishment of this cohort. Based on previous recruitment numbers of past research studies in these settings, the annual number of young people enrolled in the study is expected to be a minimum of 1000. This number will sufficiently detect even the smallest effect sizes to investigate prospectively, over three years, the course of multi-dimensional functional outcomes (social and occupational function; self-harm, suicidal thoughts and behaviours; alcohol or other substance misuse; physical health)[15, 19] in young people presenting to youth-specific mental health services.

Data analysis plan

This Youth Mental Health Tracker study will allow us to determine prospectively, over three

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years, the course of key multi-dimensional functional and clinical outcomes, in young people presenting to youth mental health services. This includes:

1. Modelling the impacts of demographic, treatment and other key potentially modifiable moderator variables, on functional and clinical outcomes;
2. Mapping the clinical illness trajectories and pathophysiological mechanisms of young people to determine transition rates to more severe illness forms (e.g., severe depression, bipolar or psychotic disorder);
3. Investigating the differential effects of duration of exposure to antipsychotic, antidepressant, or mood-stabilising medications on physical health, clinical outcomes, and risks to self-harm or suicidal behaviour.

We will make use of high-level statistical techniques including mixed-effects/ multilevel modelling, Bayesian modelling[74-76], structural equation modelling[77], and data-driven techniques[78-80] such as hierarchical cluster analysis[81-83], latent profile analysis[84], and group-based trajectory modelling.[85]

Ethics and dissemination

The study has been reviewed and approved by the Human Research Ethics Committee (HREC) of the Sydney Local Health District (SLHD, 2019/ETH00469, protocol version v1-2, 01/07/2019). Protocol modifications will only be implemented after HREC approval.

This is a research database study, therefore, consent process is entirely concerned with permissions regarding the storage and use of routinely collected data. For this reason, an opt-out consent process has been implemented. Potential participants presenting to the service

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at the participating sites will be in-depth informed by the clinicians about the study. The opt-out consent will be conducted at an '*arm's length approach*'. Participants will have sufficient time to consider whether they would like to participate in the research project. Young people under the age of 15 will initially undergo the standard consent process. However, the young participants who do not opt-out of the study will be required to obtain additional parent/guardian consent. Participants can withdraw from the study at any time. Participants will be assured that their decision to participate will not affect their treatment, nor the current or future relationship with their treating clinician or researchers at the service. All participant data will be de-identified and stored in accordance with applicable security standards; therefore, the privacy of all participants will be protected.

Research findings will be disseminated through peer-reviewed journals and scientific conference presentations, and participant data will be non-identifiable.

This study allows to build a large transdiagnostic clinical cohort. The data can be used to model the clinical course and long-term functional outcomes of young people who present for clinical care before extensive exposure to interventions or chronic illness course. The study aims to improve identification, characterisation, and profiling of adolescent-onset mental disorders to enhance personalised interventions, and health service strategies that greatly enhance care for young people.

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Contributors

IBH conceived the research idea, designed the study, and is the principal investigator. CR and YJCS contributed to study conception and wrote the study protocol with input of IBH, JJC, TAD, FI, BH, NZ, AN, JSC, AMT, CW, SPC, AJG, DK, FML, EMS. CR wrote the manuscript with input of IBH, YJCS, JJC, TAD, FI, BH, NZ, AN, JSC, and AMT. All authors critically reviewed content and approved the final version of the publication.

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Competing interests

Project Synergy (2014–2016) was commissioned by the Department of Health and conducted by the Young and Well Cooperative Research Centre (Young and Well CRC) in partnership with the University of Sydney's Brain and Mind Centre. The Department of Health (Australian Government) has further supported Project Synergy through a significant investment over 3 years (2017–2020) which led to the development of InnoWell Pty Ltd, a joint venture between the University of Sydney and PricewaterhouseCoopers (Australia) (PwC). The University of Sydney and PwC (Australia) each have a 45% shareholding in InnoWell. The remaining 10% shareholding is evenly shared between Professor Jane Burns and Professor Ian Hickie.

Legends

Figure 1: Overview of study visits. After completing the baseline visit, participants will be followed-up once yearly. During each visit, self-report questionnaires and clinical routine assessments have to be completed. In addition, participants will be asked to complete self-report questionnaires also 3 and 6 months after study start.

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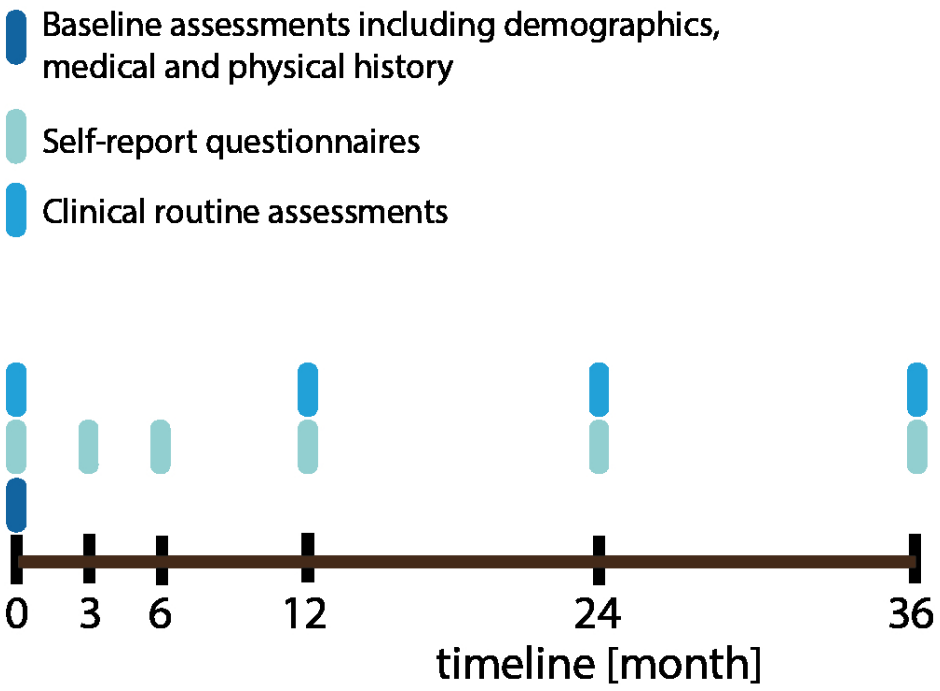

Overview of study visits. / After completing the baseline visit, participants will be followed-up once yearly. During each visit, self-report questionnaires and clinical routine assessments have to be completed. In addition, participants will be asked to complete self-report questionnaires also 3 and 6 months after study start.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on page #
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	NA
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	14
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	6-7

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Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	NA
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1, 8-12
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			**NA**

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Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13

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	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA
Methods: Monitoring			**NA**
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA

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Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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