PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Youth Mental Health Tracker: Protocol to establish a longitudinal cohort and research database for young people attending Australian mental health services.
AUTHORS	Rohleder, Cathrin; Song, Yun; Crouse, Jacob; Davenport, Tracey; Iorfino, Frank; Hamilton, Blake; Zmicerevska, Natalia; Nichles, Alissa; Carpenter, Joanne; Tickell, Ashleigh; Wilson, Chloe; Cross, Shane; Guastella, Adam; Koethe, Dagmar; Leweke, F. Markus; Scott, Elizabeth; Hickie, Ian

VERSION 1 – REVIEW

REVIEWER	Graham Thornicroft KCL UK
REVIEW RETURNED	05-Nov-2019

GENERAL COMMENTS	Youth Mental Health Tracker: Protocol to establish a longitudinal cohort and research database for young people attending Australian mental health services. This paper includes the following strengths: • A large sample size • Addresses important research questions • Very strong team • Good array of measures • Strong cohort design The paper could be improved by: • stating why people presenting to primary care are excluded ie why only those in specialist care included? • Justification of the age range included • Clarifying whether the transdiagnostic model also includes people who are sub-threshold on all diagnostic categories and who nevertheless have a substantial set of disabilities or symptoms? • Giving brief justification for these three elements: 'three underlying pathophysiological mechanisms (neurodevelopmental abnormalities, hyperarousal, circadian dysfunction) • Giving at least in outline details of the staging model that is used • Saying why, if this is a long term outcome study, individuals are tracked over only 3 years • Giving details of who is funding this study • Giving more information about the participation of young people in the cohort study as advisors/co-applicants • More information about where (ie which towns/cities etc) will be used for recruitment • Why do the team not include measures of stigma or access/barriers to care? • The section on dissemination needs to be stronger re the intended impact of the study

REVIEWER	Jonathan D. Schaefer Institute of Child Development University of Minnesota Minneapolis, MN 55455 United States
REVIEW RETURNED	27-Jan-2020

GENERAL COMMENTS	I have only minor comments on this thoughtful and innovative proposal, which all involve areas where I believe readers of the proposal would benefit from having additional information. Those areas are as follows: Study Methodology (1) What are the credentials and training of the health professionals administering the study measures, and collecting medical/physical history information at the in-person assessments? Are these all primary care providers? Will they all have specialty training in mental health? And will they be required to complete any training before administering study materials? (2) I am intrigued by the authors' proposal to examine some of the pathophysiological mechanisms that underlie many types of common mental disorders (i.e., neurodevelopmental abnormalities, hyperarousal, circadian dysfunction). Table 1 indicates that participants will complete measures on sleep timing and quality at multiple time points. However, I did not see how the authors intend to assess hyperarousal and neurodevelopmental abnormalities, or how they intend to determine that these are, in fact, directly responsible for study participants' presenting complaint. The authors should expand on this subject in the body of their proposal (rather than leaving all of the details in citations). (3) Relatedly, I think it would also be helpful to the readers if the authors provided more details regarding their "transdiagnostic clinical staging" model in the main text. In particular, I am wondering how such a model accounts (or does not account) for the comorbidity commonly seen among psychiatric disorders. Are individuals categorized into stages based solely on their most significant complaint (e.g., treating "severe depressed mood with some alcohol misuse and social anxiety" the same way as "severe depressed mood only")? Or does this model also give weight to accompanying comorbidities in some way? Inclusion/Exclusion Criteria (4) The authors report that individuals with intellectual disabilities will be excluded from this study. How will disability status be determined? (5) I am curious about the authors' claims that recruitment will not be restricted by specific diagnostic criteria, but--at the same time--that they will focus on participants with emerging mood, anxiety, bipolar, or psychotic disorders. How will recruitment and assessment of individuals with primary externalizing-spectrum conditions (e.g., ADHD, substance use disorders) be handled? Do the authors plan to track the progression of these illnesses in much the same way as internalizing and psychotic disorders? If not, why not?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
Youth Mental Health Tracker: Protocol to establish a longitudinal cohort and research database for young people attending Australian mental health services.
This paper includes the following strengths:
• A large sample size
• Addresses important research questions
• Very strong team
• Good array of measures
• Strong cohort design

Thank you very much for your positive feedback.

The paper could be improved by:
• stating why people presenting to primary care are excluded ie why only those in specialist care included?

We apologise for not being clear enough. We include patients presenting to enhanced primary care (i.e., the young people access their GP for a referral to headspace, or Early Intervention and High Intensity Services) as well as specialist care (USpace). We modified the wording in the study design and setting section to clarify.

• Justification of the age range included

The mental health service sites that are included in this study provide mental health support to a certain age bracket of young people aged 12-25 (headspace) and 16-30 (USpace), respectively. Thus, the age range is 12-30 for participation in the study. We have modified the wording accordingly

• Clarifying whether the transdiagnostic model also includes people who are sub-threshold on all diagnostic categories and who nevertheless have a substantial set of disabilities or symptoms?

Yes, the transdiagnostic model also includes people who are sub-threshold on all diagnostic categories, who have a substantial set of disabilities or symptoms. In particular, the majority of young people presenting to headspace do not yet fulfil diagnostic criteria.
To clarify, we added the following paragraph to the section “study population”:
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.

• Giving brief justification for these three elements: ‘three underlying pathophysiological mechanisms (neurodevelopmental abnormalities, hyperarousal, circadian dysfunction)

Thank you for this comment. We included the following paragraph in the introduction:
"Based on the results of a cross-sectional study31, 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 cognitive impairments, learning difficulties, and autism spectrum disorder. This subtype is based on evidence linking neurodevelopmental abnormalities with increased risk of developing psychotic phenomena32-34 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"

• Giving at least in outline details of the staging model that is used

We added a brief outline of the model (including some details regarding comorbidities as suggested by reviewer 2) to the introduction as follows:
"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 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."

• Saying why, if this is a long term outcome study, individuals are tracked over only 3 years

The individuals will only be tracked over 3 years because we only have funding and ethical approval to conduct this study for a 3 year period. However, we seek to request further funding and ethical approval to ensure we reach the longitudinal objective could be continued in an ongoing manner.

• Giving details of who is funding this study

In addition to Professor Hickie’s fellowship as indicated in the manuscript, this study is funded by a philanthropic grant administered through the University of Sydney Donor Program. The donor(s) wished to remain anonymous to fund the research project Youth Mental Health Tracker: Establishing

a longitudinal research database for the Youth Mental Health Population. We have modified the wording in the manuscript to further clarify this.

• Giving more information about the participation of young people in the cohort study as advisors/co-applicants

Thank you for noting that. We added the following sentence to the Patient and Public Involvement section: Although young people were consulted during the development of the technology used to measure relevant outcomes of the study, they were not invited to comment on the study design.

• More information about where (ie which towns/cities etc) will be used for recruitment

As stated in the study design and setting section, the study will take place at two centres in Sydney (Brain and Mind Centre, Camperdown, University of Sydney, NSW and St. Vincent's Private Hospital, Darlinghurst, NSW).

• Why do the team not include measures of stigma or access/barriers to care?

As the study objective is tracking the presentation and treatment young people receive at the selected youth mental health services, measurement of access and barriers to care are not collected at these services in a standardised manner.

• The section on dissemination needs to be stronger re the intended impact of the study

Thank you for raising this point. We have now added the following paragraph:
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.

Reviewer 2:
I have only minor comments on this thoughtful and innovative proposal, which all involve areas where I believe readers of the proposal would benefit from having additional information.

Many thanks for your kind comment.

Those areas are as follows:
Study Methodology
(1) What are the credentials and training of the health professionals administering the study measures, and collecting medical/physical history information at the in-person assessments? Are these all primary care providers? Will they all have specialty training in mental health? And will they be required to complete any training before administering study materials?

We apologise for not being clear regarding the qualification. The study takes place at enhanced primary care (headspace Camperdown, and Early Intervention and High Intensity Services) and

specialist youth mental health services, as described in the study design and setting section. We have now changed the wording to state that more clearly.
All health professionals involved in this study are mental health professionals; therefore, no additional training is necessary. We have changed the wording accordingly in the study course and procedures section. The health professionals will be adequately trained on study assessments as part of their routine care and service model.

(2) I am intrigued by the authors' proposal to examine some of the pathophysiological mechanisms that underlie many types of common mental disorders (i.e., neurodevelopmental abnormalities, hyperarousal, circadian dysfunction). Table 1 indicates that participants will complete measures on sleep timing and quality at multiple time points. However, I did not see how the authors intend to assess hyperarousal and neurodevelopmental abnormalities, or how they intend to determine that these are, in fact, directly responsible for study participants' presenting complaint. The authors should expand on this subject in the body of their proposal (rather than leaving all of the details in citations).

Thank you for this comment.
The allocation to one of the three subgroups will be done on the basis of the description of the clinical representation including historical and current symptom data (see: Hickie IB, Hermens DF, Naismith SL, Guastella AJ, Glozier N, Scott J, Scott EM: Evaluating differential developmental trajectories to adolescent-onset mood and psychotic disorders. BMC Psychiatry 2013, 13:303 and Carpenter JS, Iorfino F, Cross SP, Davenport TA, Hermens DF, Rohleder C, Crouse JJ, Leweke FM, Koethe D, Guastella AJ et al: Combining clinical stage and pathophysiological mechanisms to understand illness trajectories in young people with emerging mood and psychotic syndromes. MJA 2019, 211(9):S12-S22.). Any cases presenting with anxiety and depressive symptoms only, with no evidence of psychotic or manic features, and no indication of atypical symptoms will be allocated to the “hyperarousal-anxious depression” subtype. Cases of adolescent- onset mood and psychotic syndromes with a current primary psychotic disorder or a history of childhood- onset significant and persistent developmental difficulties (such as an autism spectrum disorder, specific learning disability, or low intelligence quotient) are allocated to the “neurodevelopmental–psychosis” illness subtype. Any cases with significant manic-like symptoms or significant atypical features (e.g., reduced activation and energy, prolonged sleep or prolonged fatigue) are allocated to the “circadian–bipolar spectrum” illness subtype.
We added the following section to the introduction to explain the proposed illness subtypes and associated pathophysiological mechanisms in more detail:
"Based on the results of a cross-sectional study31, 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 cognitive impairments, learning difficulties, and autism spectrum disorder. This subtype is based on evidence linking neurodevelopmental abnormalities with increased risk of developing psychotic phenomena32-34 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"

(3) Relatedly, I think it would also be helpful to the readers if the authors provided more details regarding their "transdiagnostic clinical staging" model in the main text. In particular, I am wondering how such a model accounts (or does not account) for the comorbidity commonly seen among psychiatric disorders. Are individuals categorized into stages based solely on their most significant complaint (e.g., treating "severe depressed mood with some alcohol misuse and social anxiety" the same way as "severe depressed mood only")? Or does this model also give weight to accompanying comorbidities in some way?

Thank you for raising that point. We added a brief description of the staging model to the introduction: "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 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."

Inclusion/Exclusion Criteria
(4) The authors report that individuals with intellectual disabilities will be excluded from this study. How will disability status be determined?

The exclusion criterion “Intellectual disability (at investigator’s discretion) was chosen to ensure that the participants are able to fill out the online questionnaires reliably. Each site will use its standard procedures for assessing the ability of the participants to fill out questionnaires by themselves reliably. We changed the wording accordingly: "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 each site) will be excluded due to inability to accurately complete study scales and questionnaires."

(5) I am curious about the authors' claims that recruitment will not be restricted by specific diagnostic criteria, but--at the same time--that they will focus on participants with emerging mood, anxiety, bipolar, or psychotic disorders. How will recruitment and assessment of individuals with primary externalizing-spectrum conditions (e.g., ADHD, substance use disorders) be handled? Do the authors plan to track the progression of these illnesses in much the same way as internalizing and psychotic disorders? If not, why not?

Thank you for this comment you raise. The young people are recruited on the basis of presentation for care. The vast majority who present to such ambulatory-care clinical services have 'internalizing' disorders *anxiety, depression, mood or psychotic disorders etc., often associated with role impairment, comorbid substance misuse and suicidal thoughts and behaviour.
The service is not an acute care service and does not recruit directly from other acute mental health settings. Hence, the proportion of persons with major 'externalizing' disorders as their primary difficulty is low.
In order to clarify we added the following paragraph to the “study population” section:
"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."

VERSION 2 – REVIEW

REVIEWER	Jonathan Schaefer Institute of Child Development, University of Minnesota United States
REVIEW RETURNED	02-Mar-2020

GENERAL COMMENTS	The authors have satisfactorily addressed my comments.