PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a Young Adult Mental Health (Uspace) Cohort: Personalising multidimensional care in young people admitted to hospital.
AUTHORS	Tickell, Ashleigh; Rohleder, Cathrin; Garland, Alexandra; Song, Yun; Carpenter, Joanne; Harel, Kate; Parker, Lisa; Hickie, Ian; Scott, Elizabeth

VERSION 1 – REVIEW

REVIEWER	Helena Tuomainen Warwick Medical School, University of Warwick
REVIEW RETURNED	27-May-2020

GENERAL COMMENTS	The paper presents a protocol for a study examining the impact of personalised multidimensional care in a cohort of young people. The protocol is well written and I have only a few comments and requests for clarification. My main query is linked to the following: On page 8 you state "However, personalised care means implementation of new protocols, training, and practice, as well as cultivating a new conceptual framework [21, 22]." Please describe how new protocols, training, practice and new conceptual framework has been/will be implemented in the Uspace clinic. Have these happened prior to the intervention linked to personalised care? Also, you mention on p. 9 that you will follow up patients for 24 months if possible. The section on assessments does not clarify whether and what assessments are completed after baseline, and how frequently, and whether these will inform the study. Objectives p. 4 Line 44 onwards: It would be helpful if the objectives of the study are presented concisely e.g. in bullet points at the beginning of the section p. 7 Line 44/45: As this is a protocol, better if this sentence is in future tense: "Personalised Multidimensional Care" study will generate p. 8 - is Uspace name of clinic or cohort? Sentence on line 7 is unclear. p. 9. Lines 13-18: Please clarify in text the RDoC approach. Please also clarify the sentence regarding the subject sample starting on line 20.

	p. 9 line 39 Patient cohort: Add (length of) recruitment period – start date and anticipated end date p. 10 Study course and procedures: Please clarify patient recruitment process – who introduces study and takes consent? p. 10 Assessments: Line 36: Please clarify how long the baseline assessment may take (days/weeks – a timeline may be helpful) and provide more clarity regarding routine clinical assessments and additional assessments due to cohort study, i.e. which assessments are additional? Can participants refuse any of the assessments? Please also clarify frequency of assessments after baseline, if applicable. As it is a cohort study, the expectation is that there will be follow-up assessments. A table summarising main outcomes of interest and measures used to assess these would be helpful for the reader p. 10- Lines 40-46: Two sentences starting “Participants are determined to have (…). These include depressive (…)” is better suited as inclusion criteria under Patient cohort on p. 9 p. 14 Sample size calculation: please provide further details of sample size calculation. The calculation should take attrition into account p. 14 Feedback and personalised care Please clarify what part of feedback and personalised care is normal routine clinical care and what is additional, as part of the study. Also, will special personalised interventions be available, by taking part in the study? Or do all patients have access to the same measurements and clinical, personalised, care? Please provide examples of personalised care/interventions. p. 14 Data analysis plan How will you deal with missing data? Will authors develop a statistical analysis plan for the cohort study before analysis?

REVIEWER	Ovidiu Popa-Velea University of Medicine and Pharmacy Carol Davila Faculty of Medicine Department of Medical Psychology Bucharest, Romania
REVIEW RETURNED	04-Jul-2020

GENERAL COMMENTS	This study protocol is interesting and intrinsically valuable (through its multidimensionality, focus on young individuals, and intention to contribute to the building of new effective models of personalized care). A number of details can be still improved to ensure a better accuracy of the protocol: #1. Research question and study objective

	The authors should clarify if the aim of the protocol is strictly exploratory, or is based on specific hypotheses (in the latter case, they should be clearly defined). #6. Outcomes The utility of the study as a whole could be more clearly defined, avoiding general terms (page 5, rows 30-44). #7. Statistics A more accurate description of the statistical methods is needed. It would be also useful to know how the authors intend to statistically handle dropouts in this study (have they already been considered in the sample size calculation?) Given the high number of administered tests, the authors should offer additional information about how they plan to ensure compliance / motivation of study participants, especially taking into account their affective imbalance.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

My main query is linked to the following: On page 8 you state “However, personalised care means implementation of new protocols, training, and practice, as well as cultivating a new conceptual framework [21, 22].” Please describe how new protocols, training, practice and new conceptual framework has been/will be implemented in the Uspace clinic. Have these happened prior to the intervention linked to personalised care?

We have started implementing new protocols, training, and practice, and cultivated a new conceptual framework already, and established the use of technology and neurocognitive testing as standard clinical care in the Uspace clinic. In our previous feasibility study, we showed that it is possible to establish the use of technology and neurocognitive testing as standard clinical care (reference 21: Tickell, A.M., et al., *Developing neurocognitive standard clinical care: A study of young adult inpatients.* Psychiatry Res, 2019. **276**: p. 232-238.). Based on these results, we decided to add further routine assessments (e.g., circadian assessments, metabolic and hormonal profiling) to the standard clinical care.

In the current study, we will investigate if these additional routine assessments meet our expectations and optimise clinical outcomes by providing personalised and measurement-based care.

In order to clarify this point, we have amended the manuscript as follows:

We have previously shown that it is feasible to integrate technology and neurocognitive testing as standard clinical care in an inpatient unit, and that neurocognitive profiling may help us to better understand the illness severity in young patients [21]. Based on these results, we have decided to add further routine assessments (e.g., circadian, metabolic, and hormonal profiling) to be able to routinely provide personalised and measurement-based care.

Also, you mention on p. 9 that you will follow up patients for 24 months if possible. The section on assessments does not clarify whether and what assessments are completed after baseline, and how frequently, and whether these will inform the study.

With the patient's consent we will invite patients back for a follow-up study. The assessments conducted at baseline will be done at 24 months. This will inform a unique tracking of the patients from a inpatient facility. However, since our manuscript submission we are in the process of an ethics amendment to include an additional 6 month and 12 month follow-up to improve the care provided as we have found this to be effective in previous experience with other studies. We have changed the wording accordingly.

p. 4 Line 44 onwards: It would be helpful if the objectives of the study are presented concisely e.g. in bullet points at the beginning of the section

Thank you for your suggestions and apologise for the oversight. We have now added the objectives of the study as bullet points to the section.

The objectives of the study are:

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

p. 7 Line 44/45: As this is a protocol, better if this sentence is in future tense: "Personalised Multidimensional Care" study will generate

We have changed the wording as suggested.

p. 8 - is Uspace name of clinic or cohort? Sentence on line 7 is unclear.

We apologise for the confusion, USpace is the name of the clinic and, thus, we named our cohort Uspace cohort.

p. 9. Lines 13-18: Please clarify in text the RDoC approach. Please also clarify the sentence regarding the subject sample starting on line 20.

We have amended the section to clarify the RDoC approach and the study population as follows:

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

The recruitment will be based on the presentation to care and is not restricted by specific diagnostic criteria. The diagnosis-independent selection of participants as well as the comprehensive assessments are consistent with the transdiagnostic 'Research Domain Criteria' (RDoC) approach [24]. RDoC aims

to classify mental disorders based on neurobiological and behavioural measures that cut across current disorder categories. The use of functional, circadian, hormonal, metabolic, and cognitive assessments, allows to attain a comprehensive picture of the individuals admitted to USpace, and a subsequent classification based on biobehavioral dimensions. Furthermore, as this study is offered young people admitted to Uspace independent from diagnosis (i.e., we will not exclude young people with a primary diagnosis outside a target category, a co-morbid disorder or those who have some, but not all of the criteria required for a diagnosis of a specific disorder), our resulting cohort will have the appropriate variance as advocated by proponents of the RDoC approach [25]. However, the vast majority of young people admitted to USpace will have a primary diagnosis of an affective disorder. These include depressive disorder, anxiety disorder, bipolar disorder, or affective psychosis.

p. 9 line 39 Patient cohort:

Add (length of) recruitment period – start date and anticipated end date

Meanwhile the study has already commenced and we have added the start date (March 2020) in the study design and setting section, whereby we have described that the study will be conducted over a period of 5 years.

p. 10 Study course and procedures:

Please clarify patient recruitment process – who introduces study and takes consent?

We added the following sentence to specify who will introduce the study. The consenting process is described in the Ethics and Dissemination section.

Potential participants who are admitted to USpace and interested in participating will be referred to the research study at arms-length. The participant will then be in-depth informed by research staff based at the clinic to introduce the study and undertake consent.

p. 10 Assessments:

Line 36: Please clarify how long the baseline assessment may take (days/weeks – a timeline may be helpful) and provide more clarity regarding routine clinical assessments and additional assessments due to cohort study, i.e. which assessments are additional? Can participants refuse any of the assessments? Please also clarify frequency of assessments after baseline, if applicable. As it is a cohort study, the expectation is that there will be follow-up assessments.

A table summarising main outcomes of interest and measures used to assess these would be helpful for the reader

We apologise that the timeline was not presented clearly.

All assessments will be completed within 2-3 weeks (including circadian assessments) after admission to USpace.

Hormonal and metabolic measures are routinely collected at Uspace on admission as a patient.

Based on our experience, most participants are booked in to complete neurocognitive testing and self-report questionnaires within four days of admission.

Neurocognitive testing (CANTAB) will take 40 to 50 minutes. Depending on the health condition of the participants, the testing can be split and done over two consecutive days. However, based on our experience it is seldom required.

The self-report questionnaire will be completed the day after neurocognitive testing. It will take approximately 45 to 60 minutes. As for the neurocognitive assessments, it is possible to complete the questionnaire on two consecutive days if necessary.

We added a table to clarify the timeline of the assessments. Furthermore, we pointed out more clearly which assessments are done as part of the clinical routine and which are only offered to participants of the study.

p. 10- Lines 40-46: Two sentences starting “Participants are determined to have (...). These include depressive (...)” is better suited as inclusion criteria under Patient cohort on p. 9

Thank you for your suggestion. We integrated the sentences in the patient cohort section.

p. 14 Sample size calculation: please provide further details of sample size calculation. The calculation should take attrition into account

We added follwing details to the sample size calculation section:

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

p. 14 Feedback and personalised care

Please clarify what part of feedback and personalised care is normal routine clinical care and what is additional, as part of the study. Also, will special personalised interventions be available, by taking part in the study? Or do all patients have access to the same measurements and clinical, personalised, care? Please provide examples of personalised care/interventions.

We apologise that this was not made clear. The uniqueness of this clinic setting and inpatient facility is that most of the normal routine care is personalised care. Therefore, to be able document and publish this protocol and to investigate research questions on this cohort is critical. All measurements discussed are a part of normal routine care, except the self-report questionnaires. However, more recently the clinical staff have found the self-report data valuable and informative in providing patient care. Therefore, we are current working towards embedding this as normal routine care.

p. 14 Data analysis plan

How will you deal with missing data?

Will authors develop a statistical analysis plan for the cohort study before analysis?

We added the following section to describe how we will deal with missing data:

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

As this is an observational study, we will not develop an additional formal statistical analysis plan. However, we added more details to the data analysis plan section of the protocol paper to describe our analytical strategies. The detailed description of our planned analyses contributes to an increased transparency and validity of the future findings, as the protocol paper will be published prior to the completion of the study.

Besides the additional paragraph regarding the handling of missing data mentioned above, we amended the section as follows:

As the data collected will be highly multidimensional, aside from the use of standard statistical approaches (e.g. ANOVA, correlations, regression), we will employ more advanced statistical techniques to investigate the underlying interactions between demographics, clinical presentation, neurocognition, sleep-wake profiles, and metabolics profiles in driving mental and physical ill-health. These approaches include mixed-effects modelling as this is suited to data where samples are observed repeatedly, Bayesian modelling as this can be used to estimate the level of uncertainity in our parameter estimations [44, 45], structural equation modelling [46], and more data-driven techniques [47-49] such as hierarchical cluster analysis [12, 21, 50], latent profile analysis [51], and group-based trajectory modelling [52] will be applied. To take advantage of the multidimensional and longitudinal nature of the data collected, machine learning approaches can be used to build models predictive, at baseline, of downstream physical and mental ill-health outcomes. Algorithms that also provide some transparency in variable importance such as tree-based algorithms (Random Forest, XGBoost) and penalised regression (LASSO, Elastic-net) will be suitable for this.

#1. Research question and study objective

The authors should clarify if the aim of the protocol is strictly exploratory, or is based on specific hypotheses (in the latter case, they should be clearly defined).

We apologise for not making this clearer and have now clarified the aim of our cohort study and included specific objectives.

#6. Outcomes

The utility of the study as a whole could be more clearly defined, avoiding general terms (page 5, rows 30-44).

Thank you for your suggestions. We have added the objectives of the study as bullet points at the beginning of the Objectives of the Study and Conceptual Framework section.

#7. Statistics

A more accurate description of the statistical methods is needed. It would be also useful to know how the authors intend to statistically handle dropouts in this study (have they already been considered in the sample size calculation?)

As described above, we have added a more accurate description of the statistical methods, including a section describing how we will handle missing data.

Given the high number of administered tests, the authors should offer additional information about how they plan to ensure compliance / motivation of study participants, especially taking into account their affective imbalance.

The assessments are not done on one day but completed within a 2-3 week timeframe (including circadian profiling), as typically admissions are on average 3 weeks. To describe the timeframe of the assessments more clearly, we added a table in the “Study course and procedures section”. Neurocognitive testing will take 40-50 minutes, the self-report questionnaires can be completed within 45-60 minutes. Furthermore, they can be split and completed on two consecutive days if this is required due to the health condition of the participants. We ensure that this is not a honerous or enforced participation. Based on our experience, the feedback session of their personalised data keeps the participants engaged, during which the results of the assessments are explained and discussed.

VERSION 2 – REVIEW

REVIEWER	Helena Tuomainen Warwick Medical School, University of Warwick, UK
REVIEW RETURNED	30-Sep-2020

GENERAL COMMENTS	I am happy with the revisions, but have a few more queries. Can you please clarify how the care of the young people taking part in the study differs from those who don't take part, i.e. from usual care. As I currently understand it, study participants are offered additional measurements and assessments as compared to usual care, and hence, will receive more detailed feedback from their clinician and more personalised care. It would have been helpful to see a table highlighting usual assessments vs additional assessments, but this is not essential. Also, how long is recruitment planned for? Please provide estimated end date of recruitment. A third minor comment: What is the average length of stay in the Upace unit? Is it expected that (all/most) follow-up assessments will happen after discharge? Minor edits: Page 6 Line 48: Is follow-up at 24 months a separate study or part of the existing one? I would call it a follow-up assessment (not study). Lie 52: an inpatients facility (an) Page 8, Line 13: explain what you mean with ‘at arms-length’ Page 14: Line 26: Improve sentence

REVIEWER	Ovidiu Popa-Velea Department of Medical Psychology Faculty of Medicine University of Medicine and Pharmacy Carol Davila Bucharest, Romania
REVIEW RETURNED	10-Sep-2020

GENERAL COMMENTS	Compared to the first version, the revised protocol is clearer and addresses all the problematic points identified before. The manuscript could be accepted for publication in its current form.	

VERSION 2 – AUTHOR RESPONSE

Reviewer 1:

I am happy with the revisions, but have a few more queries. Can you please clarify how the care of the young people taking part in the study differs from those who don't take part, i.e. from usual care. As I currently understand it, study participants are offered additional measurements and assessments as compared to usual care, and hence, will receive more detailed feedback from their clinician and more personalised care. It would have been helpful to see a table highlighting usual assessments vs additional assessments, but this is not essential.

The only difference for young people taking part in the study is that we offer to fill out an additional self-report questionnaire and that the results will be discussed in detail in the feedback session. All other assessments have already been implemented in the daily routine during the last years. However, the current study will help us evaluate if these additional routine assessments meet our expectations and optimise clinical outcomes by providing personalised and measurement-based care. To highlight the difference between the current standard routine assessments and the new additional assessments, we have modified the subheadings in table 1.

Also, how long is recruitment planned for? Please provide estimated end date of recruitment. The study will be conducted over a period of 5 years. Due to the 24-months follow-up, the recruitment phase will be 3 years. We have added the estimated end date of recruitment and the estimated date of study completion to clarify this point.

This “Personalised Multidimensional Care” study has started in March 2020 and will be conducted over a period of 5 years with assessments at baseline and possible longitudinal follow-up available upon participant consent up to 24 months (estimated end date of recruitment: March 2023; estimated date of study completion: March 2025). That is, with the patient’s consent, we will invite patients back for a follow-up assessment.

A third minor comment: What is the average length of stay in the Upace unit? Is it expected that (all/most) follow-up assessments will happen after discharge?

Yes, the average stay is 10-14 days. Therefore we expect that almost all follow-up assessments will happen after discharge. We changed the wording as follows:

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

Minor edits:

Page 6 Line 48: Is follow-up at 24 months a separate study or part of the existing one? I would call it a follow-up assessment (not study). Line 52: an inpatients facility (an)

Page 8, Line 13: explain what you mean with ‘at arms-length’

Page 14: Line 26: Improve sentence

Thank you very much for reviewing so carefully.

Page 6: We have changed the wording as suggested.

Page 8: Arms-length approach is a recruitment strategy that is an ethical principle used in Australian clinical trial standards, to ensure that there is minimal perceived coercion from the referring clinician to the participant to participate in the study. We changed the wording as follows to explain this approach:

Potential participants who are admitted to USpace and interested in participating will be referred to the research study at arms-length to ensure that there is minimal perceived coercion from the referring clinician to the participant to participate in the study.

Page 14: We modified the sentence as follows:

Once the participants have completed the self-report assessment, the data is collated and displayed as a detailed and immediate dashboard of results.

VERSION 3 – REVIEW

REVIEWER	Helena Tuomainen Warwick Medical School, University of Warwick, UK
REVIEW RETURNED	30-Oct-2020

GENERAL COMMENTS	Thanks for the clarifications and revisions. I have no further comments.