PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	What are the health outcomes of trans and gender diverse young people in Australia? Study protocol for the Trans20 longitudinal cohort study
AUTHORS	Tollit, Michelle Anne; Pace, Carmen C; Telfer, Michelle; Hoq, Monsurul; Bryson, Janet; Fulkoski, Nicholas; Cooper, Charlie; Pang, Ken

VERSION 1 – REVIEW

REVIEWER	Michael Goodman Emory University
REVIEW RETURNED	17-Jul-2019

GENERAL COMMENTS	The study protocol is well described; however, I would like offer a few suggestions: 1. The only limitation highlighted in the protocol is absence of a control group. The authors indicate that evaluating an untreated control group is not possible due to ethical reasons. It is not entirely clear what these ethical considerations might be. 2. It appears no data will be collected directly from medical, laboratory or pharmacy records. Is this the case? If so, it would be good to offer a justification. 3. It is not entirely clear if the study incorporates any data quality checks or quantitative methods of correcting systematic error from loss to follow up, missing responses or misclassification. Thank you for the opportunity to review this paper.

REVIEWER	Kate Millington Clinical Fellow Division of Endocrinology Boston Children's Hospital United States
REVIEW RETURNED	22-Jul-2019

GENERAL COMMENTS	I agree with the authors that information about the TGD community, such as they propose to obtain here, is badly needed. It also seems that they are in a good position to collect this data given the size and reach of their clinic. A few points: 1. How do you plan to incentivize patients to complete the follow up questionnaires after they have been discharged from the clinic? There aren't any incentives for participation mentioned, so I assume you are not offering any. An email survey (at least in our population) would be easily missed an unlikely to be completed.

	2. Please estimate what proportion of the population recruited would be in each age range. The ages included (3 - 17) are very diverse, have different needs, and different outcomes. 3. The authors should be more specific about the benefits this study will have for the TGD population and for their medical care. 4. Is there a protocol for responding to emergencies that may arise on the questionnaires (i.e. suicidal ideation)? 5. The article does a decent job of enumerating the subject areas for the scales, but does not tell us why these ares were chosen for focus. 6. At what intervals are they physiologic data collected? How exactly will follow up data be obtained for these?

VERSION 1 – AUTHOR RESPONSE

Comments to the Author	**Response from Authors**
Reviewer 1	
1. The only limitation highlighted in the protocol is absence of a control group. The authors indicate that evaluating an untreated control group is not possible due to ethical reasons. It is not entirely clear what these ethical considerations might be.	Thanks for making this point. We have modified the text in the discussion to more clearly describe the ethical considerations of including an untreated control group: "Furthermore, it is not ethically possible to incorporate an untreated control group in the Trans20 study design. This is because withholding treatment for the purposes of forming a comparison group may cause patients significant distress and therefore pose significant risk of harm to individuals. Absence of a control group will limit the potential to draw direct conclusions about the effectiveness of interventions but, where possible, measures with population-based data are used in Trans20 to compare outcomes of TGD youth with those of the general population. "
2. It appears no data will be collected directly from medical, laboratory or pharmacy records. Is this the case? If so, it would be good to offer a justification.	As described under the subheading *Physiology* the RCHGS clinicians routinely monitor a variety of physiological parameters, including height, weight, body mass index, blood pressure, bone mineral density, luteinising hormone, follicle stimulating hormone, testosterone, oestrogen, liver function, haemoglobin, serum cholesterol, and haemoglobin A1c. These data are stored within the EMR (for current patients) and will be directly extracted to facilitate analysis. For those who no longer attend the RCHGS, this information will be sought from patients' current treating clinician. We feel that the aforementioned existing text addresses the reviewers comment – and therefore no further action is required.
3. It is not entirely clear if the study incorporates any data quality checks or quantitative methods of correcting	To clarify, data cleaning and quality checks are an integral part of our data management procedures, and are already

systematic error from loss to follow up, missing responses or misclassification.	occurring, including manually checking a sample of responses against a computerized classification. In case of systematic error from loss to follow up, sampling weights will be used. If data is missing at random, generalised estimating equations or multiple imputation methods will be used. This is now referred to in the paper as follows: "Appropriate statistical methods will be applied to analyse the repeated measures of factors over time, their effect on the outcomes including missing data if necessary."
Reviewer 2	
1. How do you plan to incentivize patients to complete the follow up questionnaires after they have been discharged from the clinic? There aren't any incentives for participation mentioned, so I assume you are not offering any. An email survey (at least in our population) would be easily missed an unlikely to be completed.	Thank you for this comment. We have recently received additional funding and ethics approval to provide a $20 voucher to participants once surveys are completed. This is now included under "Data collection and storage": "Parent, patient and in-clinic questionnaire responses (and scored summary data where relevant) are uploaded to patients' electronic medical record (EMR) and the RCHGS Clinical Database (DRN #DB089). Thus, these are available to their treating team to help guide assessment and treatment. For those who consent to being part of Trans20 following discharge from the RCHGS, follow-up questionnaires are administered via LimeSurvey and stored in the RCHGS Clinical Database. For those discharged from RCHGS a $20 gift voucher will be offered as a sign of appreciation and as reimbursement for the time spent completing the surveys. "
2. Please estimate what proportion of the population recruited would be in each age range. The ages included (3 - 17) are very diverse, have different needs, and different outcomes.	We have addressed this query regarding the age breakdown of patients under the subheading "Participants and eligibility" as follows: "To be eligible for inclusion in Trans20, participants need to have attended an initial appointment with the RCHGS between February 2017 - February 2020, have completed at least one of the baseline questionnaires (i.e., patient questionnaire, parent questionnaire, or in-clinic questionnaire), and speak sufficient English to complete the questionnaires. Since patients can be referred to the RCHGS at any age before 18 years, participants are expected to range in age from 3-17 years at study entry. Data from the first two years of the study indicate that on the day of first appointment with the RCHGS, the large majority of patients (75.3%) were aged 12 years or older, 18.6% were aged 6-11 years and 6.1% were aged 5 years or younger. Based on

	those meeting eligibility for involvement in Trans20 in the first two years, it is expected that the Trans20 cohort will comprise approximately 600 participants over the three-year enrollment period."
3. The authors should be more specific about the benefits this study will have for the TGD population and for their medical care.	We have modified the discussion to highlight how the TGD community may benefit from the knowledge generated from this study, as follows: "In conclusion, referrals of TGD children and adolescents for medical care have been increasing across the Western world, and the current demand for transgender health services may be just the tip of the iceberg. Looking ahead, it will be paramount to fill existing knowledge gaps and determine empirically how best to manage the care of TGD young people so that future best practice guidelines can be based on as much robust evidence as possible. In this regard, the Trans20 study will provide critical information pertinent to clinical practice and its provision. It will provide integral information on the natural history of gender diversity, which will enable clinicians to provide accurate prognostic information to patients and families, and therefore assist decision-making around social and legal transition for TGD young people. The study will also provide important information on the benefits and risks of current clinical pathways which could be used to inform the TGD community about the long-term safety and outcomes of different forms of medical interventions available to them. Finally, the longitudinal nature of Trans20 will allow opportunities for targeted interventions to be identified and ultimately help to improve care for this vulnerable population."
4. Is there a protocol for responding to emergencies that may arise on the questionnaires (i.e. suicidal ideation)?	As described under the "Data collection and storage" section, information on community supports are provided at the end of all questionnaires. As some questions are completed as part of standard clinical care, clinicians involved in their care are able to provide appropriate follow up when required. We have a process in place to follow up those who are discharged who disclose clinically significant risk through the questionnaire. This is now included under the "Data collection and storage" section of the protocol as follows: "Parent and patient questionnaires are administered via LimeSurvey, an online, open source, survey web application (26), supported by the RCH for clinical use. Separate parent and patient questionnaire links are sent to a parent

	email address, and parents and patients complete the questionnaires online. Questionnaires are administered approximately one month prior to patients' initial appointment with the service, and then at approximately 12 month intervals throughout their RCHGS episode of care. Information on community supports are provided at the end of all questionnaires. Participants (who no longer attend the RCHGS) who disclose information that raises concern about a significant risk of harm will be contacted by project staff to provide additional support. This may include: discussing additional support services, encouraging the participant to contact their general practitioner and/or access existing supports and referring the participant to external supports (including mental health triaging services) where appropriate. In-clinic questionnaires – which cover topics such as drug use, sexual health, self-harm and suicidality - are asked directly of patients at an appropriate age by clinicians during their initial appointments and responses are later entered into LimeSurvey. Having been introduced by their clinicians, these questions are subsequently asked of patients in their online follow-up questionnaires."
5. The article does a decent job of enumerating the subject areas for the scales, but does not tell us why these areas were chosen for focus.	We have adapted the text under the "Measures" section to provide further justification for measuring a broad range of data in Trans20: "Trans20 questionnaire measures were selected to provide information relevant to the assessment and treatment of GD and related co-morbidities. Measures span multiple domains including gender, mental health, education, quality of life, parental wellbeing, family functioning, as well as their experience of care at RCHGS. In addition to measuring core gender-related and mental health outcomes, broader indicators of health and wellbeing were also included to holistically and comprehensively assess multifaceted functioning (including at school and within the family) which may be related to gender and mental health outcomes in this group. Where possible, measures with strong psychometric properties and good reliability and validity were chosen."
6. At what intervals are they physiologic data collected? How exactly will follow up data be obtained for these?	As described under "Physiology", the physiological data will be collected as per standard clinical care, and as guided by the Australian Standards of Care and Treatment Guidelines for Trans and Gender Diverse Children and Adolescents (13). Patients on puberty blockers and gender affirming hormones patients are reviewed by clinicians approximately every 3-6 months. We will routinely extract physical health information generated from these appointments from patients medical record. For those who no longer attend the RCHGS, this information will be sought from patients' current treating clinician, at approximately the same time as their scheduled online assessments This has now been clarified in the protocol under "*Physiology"* as follows:

	“To determine the physical effects of puberty blockers and gender affirming hormones, RCHGS clinicians routinely monitor a variety of physiological parameters, including height, weight, body mass index, blood pressure, bone mineral density, luteinising hormone, follicle stimulating hormone, testosterone, oestrogen, liver function, haemoglobin, serum cholesterol, and haemoglobin A1c at regular intervals consistent with the Australian Standards of Care and Treatment Guidelines for Trans and Gender Diverse Children and Adolescent (13). These data are stored within the EMR (for current patients) and can be directly extracted to facilitate analysis. Patients on puberty blockers and gender affirming hormones are reviewed by clinicians approximately every 3-6 months, and we will routinely extract physical health information generated from these appointments from patients’ medical record. For those who no longer attend the RCHGS, this information will be sought from patients’ current treating clinician, at approximately the same time as their scheduled online assessments.”

VERSION 2 – REVIEW

REVIEWER	Michael Goodman Emory University, USA
REVIEW RETURNED	22-Aug-2019

GENERAL COMMENTS	I have no further comments.

REVIEWER	Kate Millington and Yee-Ming Chan Boston Children's Hospital, Boston MA, United States of America
REVIEW RETURNED	05-Sep-2019

GENERAL COMMENTS	The authors did a great job of incorporating our first review comments. They should make sure to add to their informed consent the possibility for intervention should participants express suicidal ideation at follow up visits, especially for participants below the age of majority.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1

"I have no further comments."

Response: No changes required

Reviewer 2

"The authors did a great job of incorporating our first review comments. They should make sure to add to their informed consent the possibility for intervention should participants express suicidal ideation at follow up visits, especially for participants below the age of majority."

Response: Thank you for this comment. Our existing informed consent statements actually mention this already, and we have now amended the manuscript to reflect this. Specifically, we now mention that for: i) participants who no longer attend the RCHGS, they are advised (via the information statements that accompany surveys) that they may be contacted for the purpose of providing additional support; and ii) for current patients with the RCHGS, appropriate follow up occurs either in-clinic or when deemed clinically relevant. These changes are shown below and can be seen under "Data collection and storage" in the manuscript.

"Parent and patient questionnaires are administered via LimeSurvey, an online, open source, survey web application (26), supported by the RCH for clinical use. Separate parent and patient questionnaire links are sent to a parent email address, and parents and patients complete the questionnaires online. Questionnaires are administered approximately one month prior to patients' initial appointment with the service, and then at approximately 12 month intervals throughout their RCHGS episode of care. Information on community supports are provided at the end of all questionnaires. Participants (who no longer attend the RCHGS) who disclose information that raises concern about a significant risk of harm will be contacted by project staff to provide additional support. This may include: discussing additional support services, encouraging the participant to contact their general practitioner and/or access existing supports and referring the participant to external supports (including mental health triaging services) where appropriate. The information statements that accompany the surveys, advises parents and participants that they may be contacted for this purpose. If individuals remain upset after completing questionnaires they are also advised to call the RCHGS to help organize support.

In-clinic questionnaires – which cover topics such as drug use, sexual health, self-harm and suicidality - are asked directly of patients at an appropriate age by clinicians during their appointments and responses are later entered into LimeSurvey. These questions are asked by clinicians during appointments to ensure timely and appropriate follow-up if required. Having been introduced by their clinicians, these questions are subsequently asked of patients in their online follow-up questionnaires, with clinicians applying appropriate follow-up for current patients as deemed clinically relevant."