



STUDY PROTOCOL

REVISED Protocol: New approaches to managing the social deficits of Turner Syndrome using the PEERS program [version 2; peer review: 2 approved]

Jeanne Wolstencroft¹, William Mandy², David Skuse¹

¹Great Ormond Street Institute of Child Health, University College London, London, WC1N 1EH, UK

²Clinical, Education and Health Psychology, University College London, London, WC1E 6BT, UK

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Abstract

Turner Syndrome (TS) is a sex chromosome aneuploidy (45,X) associated with social skill difficulties. Recent clinical care guidelines recommend that the Program for the Education and Enrichment of Relational Skills (PEERS) social skills intervention programme be trialled in this population. PEERS has been successfully used in adolescents with autism spectrum conditions without intellectual disabilities. The PEERS program will be piloted with adolescents and young women with TS aged 16-20 using an uncontrolled study trial with a multiple-case series design. The program will be delivered face to face and online. The assessment battery is designed to measure social skills comprehensively from diverse informants (parent, teacher young person). It includes measures of social performance, social knowledge and social cognition. Parents and young people taking part in the intervention will also feedback on the acceptability and feasibility of the pilot. The outcomes of this small scale pilot (n=6-10) will be used to adapt the programme based on feedback and estimate the sample for a future randomised controlled trial.

Keywords

social skills training, social skills, peers, turner syndrome, sex chromosome aneuploidy

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Open Peer Review

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- 1 **David E. Sandberg** , University of Michigan, USA
- 2 **Claus H. Gravholt** , Aarhus University Hospital, Denmark

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Jeanne Wolstencroft (j.wolstencroft@ucl.ac.uk)

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REVISED Amendments from Version 1

The protocol has been updated with clarifications suggested by the reviewers. These include precisions on the trial's inclusion criteria such as hearing ability and karyotype, as well as precisions on the level of social ability and the screening measure subscales used to detect these.

In the response to reviewers we discuss the variability of social ability within girls with TS and justify the value of piloting the PEERS program with a small group of participants before embarking on a full-scale randomized-controlled trial.

We have also updated some of the outcome measures used in the trial, for example, we originally stated that we'd used the second edition of the TASSK-R, but upon realizing that they were not widely available we are now using the first edition of the questionnaire (TASSK). We have also replaced the 'Quality of Play Questionnaire' for the 'Quality of Socialization Questionnaire' as it is more appropriate for the age-group of our participants.

See referee reports

Introduction

Turner Syndrome (45,X; TS) is one of the most common sex chromosome aneuploidies, with an incidence of 1 in 2500 female births¹. TS is associated with a variety of morbidities affecting nearly every bodily system, including skeletal abnormalities such as short stature, dysmorphic features, hearing difficulties, infertility, cardiac abnormalities, diabetes and thyroid problems. These difficulties have been well characterized in the literature (see Gravholt *et al.* 2017² for the most recent review) and require clinical monitoring across the lifespan.

TS females have social difficulties throughout childhood, but these become more apparent in adolescence when socialisation becomes more complex³. Social deficits are exemplified by difficulties integrating within social groups, with poor deciphering and processing of social cues³. Previous research has shown TS is associated with specific deficits in social cognitive competence, especially forming and maintaining peer relationships⁴.

Some of the social deficits observed in TS are reminiscent of difficulties associated with Autism Spectrum Disorders (ASD). Psychosocial evaluations of young women with TS have found an association with ASD⁵⁻⁹, anxiety disorders, depression and low self-esteem¹⁰⁻¹³.

Social skills deficits are known to have a significant impact on academic, adaptive and psychological functioning¹⁴⁻¹⁷, and are likely to have a substantial impact on the wellbeing of girls and women with TS across the lifespan³. At present, psychosocial intervention research with young women with TS is scarce; only one intervention targeting self-esteem in adults aged 18-30 has been documented in the literature¹⁰. The latest TS Clinical Care Guidelines recommend that a social skills training intervention should be trialled in this population². They suggest using the Program for the Education and Enrichment of Relational Skills (PEERS) developed for children

with ASD¹⁸. There is good evidence for the efficacy of PEERS when delivered with children and young adults with ASD without intellectual disabilities¹⁹⁻²⁴. This pilot project will be the first to examine the feasibility and acceptability of the PEERS Protocol in adolescents with TS.

Protocol**Objectives and hypothesis**

The main objectives of the study are:

- 1) To pilot the PEERS intervention in adolescents with TS;
- 2) Assess its feasibility and acceptability to families.

We hypothesise social skills training will improve social competence with peers and may produce secondary improvements in social cognition, self-esteem and anxiety (social and generalised).

Study design

We will be employing an uncontrolled trial design. To maximise the clinical reliability of the trial we will use a systematic multiple-case series design with case tracking. We aim to recruit participants with a similar degree of social impairment, and intellectual ability.

Sample size

A sample size of 6-10 girls and their parents will be invited to take part in the study - this is the group size recommended by the PEERS intervention manual. At present the effect size for this intervention in girls with TS is unknown. This pilot will serve as the basis to estimate the intervention's effect size and sample size for a future randomised control trial.

Study centres/Recruitment

Participants will be recruited from the *Social Skills and Relationships in Turner Syndrome Study* (SOAR), which recruits children and young women with TS from the Turner Syndrome Support Society, the NHS Great Ormond Street Hospital and the NHS University College London Hospitals.

The SOAR study is conducting online mental health and social cognition questionnaires with 200 girls and young women with TS and their parents. A subset of families from this large cohort that meet the trial's inclusion criteria will be invited to take part in the intervention study.

Participant inclusion and exclusion criteria

Inclusion criteria for the intervention include: 1, a confirmed diagnosis of TS (monosomy, variant, mosaic etc.); 2, age 16-20 years; 3, significant social skills difficulties as screened for in the SOAR online questionnaires (see screening assessment measures section for details) and clinical judgement; 4, motivation to take part.

The exclusion criteria for the intervention include: 1, profound hearing or vision impairments (eg. complete deafness or blindness); 2, intellectual disability (VIQ<70); 3, concurrent participation in other psychological treatment.

Intervention

The UCLA PEERS for Adolescents is a manualized treatment program that consists of 14 90 min sessions¹⁸. The program runs two concurrent groups, one for the adolescents and one for parents. At the end of each session the two groups are reunited for review and questions. Between sessions the adolescent group are given homework tasks, which they are to complete with the help of their parent who is trained to support them as their social coach. Parents are provided with concise handouts for each session, which include an overview of the lesson material and the homework.

The adolescent group sessions are structured to provide didactic instruction as well as social skill rehearsal. The parent sessions mirror the adolescent sessions and provide a space for the parents to problem-solve any difficulties they may have encountered the previous week. The didactic lessons provide instruction on (a) conversational skills; (b) electronic forms of communication; (c) developing friendship networks and finding sources of friends; (d) appropriate use of humour; (e) peer entry strategies; (f) peer exit strategies; (g) organizing get-togethers with friends; (h) handling teasing and embarrassing feedback; and (i) resolving arguments with friends¹⁸.

The adolescents and parents will attend separate concurrent sessions led by a certified PEERS Instructor. Three face to face sessions will take place in London at the start, middle and end of the program. All other sessions will be conducted online using a virtual meeting room. The face to face sessions will deliver two PEERS lessons, whereas the weekly online sessions will deliver one lesson. Research assistants (graduate or undergraduate psychology students) will monitor treatment fidelity, assist with role-playing demonstrations, and provide social coaching with performance feedback during behavioural rehearsal exercises. All research assistants will be trained and supervised throughout the intervention.

Assessments

Participants will complete assessments at different time points throughout the study. The study will last 9 months in total, including a 3 month baseline, 2 months of intervention and a 3 month follow-up period. The screening measures will be delivered at T=0, the baseline assessments will be delivered at T=12 weeks and the post intervention assessments will be delivered at T=20 weeks. The primary outcome measure will be delivered at regular intervals of 4 weeks throughout the course of the study (see Table 1).

Screening assessments

Development and Wellbeing Assessment (DAWBA): The DAWBA will be used to collect information on the child’s behavioural adjustment and mental health. The DAWBA has been used both in UK national and international surveys^{25–28}. The DAWBA data will be reviewed by a psychiatrist in accordance with the ICD-10/DSM-V diagnostic criteria. This methodology has been used successfully to gather data of high quality by parental online report. The DAWBA autism module includes a social aptitude scale (SAS) which measures social understanding and social ability (Liddle *et al.*, 2009). Participants displaying

Table 1. Assessment timeline. Informants for each assessment are included in brackets (P – Parent; T – Teacher; YP – Young Person). Assessment acronyms: BAI – Beck’s Anxiety Inventory; IAQ – Intervention Acceptability Questionnaire; PEERS – Program for Education and Enrichment of Relational Skills; PEERS QSQ – PEERS Quality of Socialisation Questionnaire; PEERS TASSK – PEERS Test of Adolescent Social Skills Knowledge; RSE – Rosenberg Self-esteem Scale; SCP – Social Competence with Peers; SDQ – Strengths and Difficulties Questionnaire; SRS – Social Responsiveness Scale; SASI – Schedules for the Assessment of Social Intelligence; SWS – Spence Social Worries Scale; WAIS-Wechsler Adult Intelligence Scale.

Timeline	Assessments
t=0	SCP (P) 1 PEERS Screener (P,YP) SASI (YP) WAIS (YP)
4 weeks	SCP (P) 2
8 weeks	SCP (P) 3
Baseline 12 weeks	SCP (P,YP,T) 4 SWS (P,YP,T) PEERS QSQ (P) PEERS TASSK (YP) RSE (YP) BAI (YP) SRS (P,T) SDQ (P,T)
16 weeks	SCP (P) 5
Post-intervention 20 weeks	SCP (P) 6 SWS (P,YP,T) PEERS QSQ (P) PEERS TASSK (YP) RSE (YP) BAI (YP) SRS (P,T) SDQ (P,YP,T) IAQ (P,YP) SASI (YP)
24 weeks	SCP (P) 7
28 weeks	SCP (P) 8
Follow-up 32 weeks	SCP (P,YP,T) 9

significant difficulties in the SAS will be eligible for the intervention. The DAWBA is available in 26 languages. The DAWBA will be completed online by parents.

Strengths and Difficulties Questionnaire (SDQ): The SDQ is a brief behavioural screening questionnaire²⁹. The SDQ includes scales that measure emotional symptoms, conduct problems, hyperactivity/inattention difficulties, peer relationship problems

and prosocial behaviour. The first four scales are combined to create a total difficulties score. An additional impact scale measures the impact of this composite score on daily life. Participants scoring poorly on the peer relationships subscale will be eligible for the intervention. It has been validated for use in children aged 4–17 in UK National studies of psychological adjustment, and a new form for 18+ years old has recently been developed. It will be completed online by the adolescents, parents and teachers.

Social Responsiveness Scale (SRS): The SRS measures the severity of autistic traits and the instrument has convergent validity with other ASD diagnostic tools^{30,31}. The SRS subscales measure Social Awareness, Social Cognition, Social Communication, Social Motivation, and Restricted Interests and Repetitive Behaviour. The SRS will be administered online to parents and teachers.

Health Questionnaire (HQ): The questionnaire was developed by the UCLH Turner Syndrome Life Course Project to record information about physical health, health care, education, social life, physical activity and relationships³². The self-report version of the questionnaire will be completed by adolescents.

Schedules for the Assessment of Social Intelligence (SASI): The SASI is a socio-cognitive assessment that measures facial expression recognition, face recognition memory, gaze-monitoring and theory of mind. The SASI is sensitive to subtle deficits in social cognition and has been shown to have excellent reliability and validity³³. Adolescents will be asked to complete the SASI online.

Wechsler Adult Intelligence Scale - Fourth UK Edition (WAIS-IV UK): The WAIS-IV is an IQ test which measures verbal comprehension, perceptual reasoning, working memory and processing speed. It has been widely used and validated³⁴. It will be administered to adolescents in person.

PEERS Screener: The PEERS Screener Questionnaire assesses the participant's motivation to take part in the PEERS intervention¹⁸. It will be administered to parents and adolescents over the phone or in person. Only participants motivated to take part will be considered for the intervention.

Primary outcome measures

Social Competence with Peers (SCP): The SCP assesses the consequences of young people's interactions with peers, such as the existence and duration of friendships or social invitations³⁵. A modified version of the SCP will be used to adapt the tool for use in young adults. The adolescent group and the parent group will be asked to complete the SCP at regular intervals (every 4 weeks) from baseline to follow-up. Teachers will be asked to complete the SCP at baseline, post-intervention and follow-up.

Secondary outcome measures

Strengths and Difficulties Questionnaire (SDQ): Described previously. It will be completed by the young people, parents and teachers at baseline and post-intervention.

Social Responsiveness Scale (SRS): Described previously. It will be completed online by parents and teachers at baseline and post-intervention.

Spence Social Worries Scale (SWS): The Spence Social Worries Scale is a psychological questionnaire designed to identify symptoms of social phobia and other forms of anxiety, in children and adolescents. The parent and teacher forms are reported to have excellent internal validity³⁵. It will be completed online by the adolescents, parents and teachers at baseline and post-intervention.

Schedules for the Assessment of Social Intelligence (SASI): Described previously. It will be administered online to the adolescent at baseline and post-intervention.

PEERS Test of Adolescent Social Skills Knowledge (TASSK): The TASSK is a questionnaire designed to evaluate what the participants have learned from the intervention¹⁸. This is the only outcome measure to evaluate changes in social knowledge. It will be administered to the adolescents at baseline and post-intervention.

PEERS Quality of Socialisation Questionnaire (QSQ): The QSQ is designed to evaluate the quality of young people's socialization and frequency of get-togethers¹⁸. It will be completed online by the parents at baseline and post-intervention.

Rosenberg Self-esteem Scale (RSE): The RSE scale assesses global self-esteem³⁶. It will be completed online by the adolescent at baseline and post-intervention.

Beck's Anxiety Inventory (BAI): This scale is a self-report measure used for measuring the severity of anxiety in children and adults³⁷. It will be completed online by the parent and adolescent groups at baseline and post-intervention.

Camouflaging measure (CAT-Q): The CAT-Q measures camouflaging (e.g. strategies to mask or compensate autistic characteristics) behaviour in social situations. It is comprised of 25 items and has high internal reliability in autistic adults. Its subscales measure compensation, masking and assimilation³⁸. The CAT-Q will be completed by adolescents.

Intervention Acceptability Questionnaire (IAQ): The IAQ has been developed for the study to assess parent and adolescent satisfaction with the intervention ([Supplementary File 1](#)). It will be completed by the parent and adolescent groups once the intervention has ended.

Missing data and intervention adherence

The occurrence of missing data will be reported for each questionnaire and study time point. Participant intervention adherence, planned absences and study dropouts will be recorded and reported. When possible the causes for missing data, absences or dropout will be reported. Families that miss sessions will be caught up over the phone or conference call before the next session.

Adverse events

Adverse events will be recorded.

Statistical analysis

The primary outcome measure (SCP questionnaire)¹⁶ will be analysed using visual analysis and multi-level modelling to track individual participant changes over 9 months from baseline to follow up³⁹.

The secondary outcome measures will be analysed for pre-post differences. Data will be analysed using SPSS version 22 statistical software. It is likely that we will be underpowered to detect any significant statistical differences between the pre and post intervention scores; therefore effect sizes (Cohen's d) will also be calculated. The parent, teacher and adolescent responses to the questionnaires will also be compared to investigate the consistencies between different informants.

We anticipate that adolescent informants will report the greatest positive changes compared to other informants. We also anticipate that the adolescents will report greater improvements on the social knowledge on the TASSK, than on the social performance on the SCP or SDQ (prosocial or peer scale) and social cognition on the SASI. We also expect to see secondary improvements on adolescent self-reports of anxiety on the BAI raw score, social anxiety on the SWS raw total score and self-esteem on the RSE raw total score. We expect to see an increase in camouflaging on the CAT-Q on all the subscales.

In line with previous social skills intervention research we anticipate that positive changes in social performance will be noted by the parents, but that schoolteachers will not observe a change post intervention on the SRS, SDQ and SWS. Specifically we expect parents to report improvements in the SWS total raw score, as well as improvements on the SDQ raw prosocial scale and peer difficulties scale, and improvements on the SRS social communication scale and repetitive and ritualised behaviours scale.

The acceptability of the intervention to families will be assessed using the IAQ. Descriptive statistics will be used to summarise the responses alongside a qualitative summary of the open text answers. We expect that most families will report having positive experiences of the PEERS programme. Based on previous randomised controlled trials we predict that adherence will be on average 80% and that up to two participating families may dropout (Laugeson *et al.*, 2015; Schohl *et al.*, 2014).

Ethics and dissemination

Ethics and consent

All participants (young people aged 16–20 and their parent) will give written informed consent prior to entry to the SOAR study. The study has been approved by the West London GTAC Ethics Committee (IRAS: 219817).

Dissemination

The results of the study will be disseminated at the Turner Syndrome Support Society conference, the study website, at

international research conferences and in research articles published in peer-reviewed journals.

Discussion

This is the first study to pilot a social skills training program with adolescents and young women with TS. Given the PEERS program's success with teenagers on the spectrum, it is anticipated that young women with TS will also benefit from taking part.

This pilot study has been designed to take an approach of high internal validity. This approach is appropriate given that it is a feasibility pilot conducted with a small number of participants (n=6–10), however the disadvantage of the approach is that the study has low external validity, which reduces the generalizability of the findings. This study will need to be replicated with young people with different social skills profiles, intellectual ability and hormone treatment status.

To our knowledge this will also be the first trial of PEERS delivered online and offline. TS is a rare genetic disorder and the delivery of the full program face to face would have resulted in many families being excluded due to geographical constraints. The program's acceptability to families will be assessed and this feedback will be used to inform future replications of the intervention. Should the combination of online and offline prove successful, this will enable the program to be made more widely available.

When assessing social skills it is important to employ a range of assessment tools, which assess different domains of social skills (social knowledge, performance and cognition), as well as a variety of informants^{40,41}. Meta-analyses of social skills intervention studies show that parents and young people report changes in social skills after taking part in social skills interventions. However, these improvements are rarely reported by teachers^{41,42}. There is a trend for young people to overestimate the changes in their social skills compared to other informants^{41,42}. However, a recent meta-analysis of the young person self-report measures suggests that the improvements relate to changes in their social knowledge rather than their social performance⁴¹.

The assessment battery has been designed to measure changes in social skills, in the domains of social performance, social knowledge and social cognition. These outcomes will be reported on by the parents, teachers and the young people themselves. Teachers and parents will be asked to report on changes in social performance through questionnaires. The young people will complete questionnaires which measure social performance and social knowledge, as well as an online task to measure changes in social cognition. The maintenance of any potential treatment gains in social performance will be assessed by the parent report at a 3 month follow-up.

It is likely that the adolescent and parent reports will be prone to expectancy biases⁴³. They may exaggerate treatment effects

due to their investment in taking part in the intervention. Using external observers (such as teachers or blinded study administrative assessors) is essential to help understand these biases and assess whether changes in performance generalise to other settings^{41,44}. Unfortunately, due to the small scale of this project, assessments by external observers will not be feasible.

Meta-analyses of social skills interventions for children on the autistic spectrum using the SRS have shown that the largest treatment gains are made in the social communication and repetitive and ritualised behaviours scale²¹. The changes in repetitive and ritualised behaviours may be mediated by reductions in anxiety or increases in social awareness^{21,45}. The majority of the participants included in the meta-analyses were adolescent males, therefore it remains to be seen whether these patterns of improvement will be replicated in females with TS.

This study will also use a novel measure of social camouflaging⁴⁶. Social camouflaging is a strategy adopted by people on the spectrum to manage social situations. It has been likened to wearing a ‘social mask’, where the individual puts on ‘their best self’⁴⁶. Camouflaging typically involves masking and compensating for social deficits^{46–48}. This might involve consciously performing a range of non-verbal cues such as making eye contact during conversations and imitating facial expressions and gestures, or following learnt social scripts such as using pre-prepared jokes or comments⁴⁹. Recent research suggests that

females are better at camouflaging than males^{48,50}. We anticipate that the intervention will help the participants become more aware of their camouflaging and help them to camouflage more effectively if they choose to use it as a strategy.

Conclusion

This will be the first social skills training programme trialled with adolescents and young women with TS. Should the trial prove successful, the initial results will be used to inform the sample size for a future randomised controlled trial. Additionally, neither research trials using the PEERS program exclusively in girls, nor trials delivering PEERS online have been published. Therefore, this trial may have a broader impact on the development of treatment strategies for both for young women that experience social skills difficulties (including those on the autistic spectrum), but also for broadening access to treatment by using technology.

Data availability

No data are associated with the article.

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Supplementary material

Supplementary File 1: Young Person Intervention Acceptability Questionnaire; Parent Intervention Acceptability Questionnaire.

[Click here to access the data.](#)

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Open Peer Review

Current Referee Status:  

Version 2

Referee Report 05 April 2019

<https://doi.org/10.5256/f1000research.20091.r45871>



David E. Sandberg 

Department of Pediatrics, Medical School, University of Michigan, Ann Arbor, MI, USA

I thank the authors for their responses. I have no further comments.

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 19 March 2019

<https://doi.org/10.5256/f1000research.20091.r45872>



Claus H. Gravholt 

Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark

I have no further comments. The authors have dealt with all questions raised.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Turner syndrome. Other sex chromosome abnormalities. Endocrinology, epidemiology, genetics

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Referee Report 15 January 2019

<https://doi.org/10.5256/f1000research.16884.r41839>



Claus H. Gravholt 

Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark

Wolstencroft et al presents a pilot protocol designed to improve the social cognition of adolescents with Turner syndrome (TS) based on the PEERS program. Overall, this study is very interesting and timely, given that many with TS have a social skills deficit.

I have some comments:

1. Design and sample size: uncontrolled, with the aim of including 6-10 TS. The uncontrolled design is acceptable in a pilot trial. I'm more worried about the rather low n. There is a large variability, perhaps even larger than among normal females, in the presentation of females with TS and that may not be captured satisfactorily with a n of 6-10. However, one could ask if it is at all necessary to perform a pilot study, given that this program has shown to be a success in other study groups?
2. Inclusion criteria: the inclusion criteria are rather strict, and I think that the authors will end up excluding a rather large proportion of females with TS, which is a pity. Many females that in their youth may not present with social skills difficulties, will actually do this at a later age, and I think it would be interesting to have some of these females included as well. Can females with hearing difficulties, but treated with a hearing aid, be included?
3. The intervention program, PEERS, is certainly very relevant.
4. The scales used to monitor effect seem relevant. The primary and secondary outcomes are relevantly described.
5. The intervention program seems rather massive with multiple scales and 12 times 90 minutes interventions. Have the authors considered how this will affect the participation rate in the study? I guess they must have contemplated this. Are there experience from other groups of patients? The authors expect 2 family dropouts – and if the inclusion ends at 6 families, that would then leave 4 families – hardly enough to call it a pilot study?
6. Conclusively, if this pilot study proves successful, it will be a welcome addition to the program of care established by excellence center for TS around the world.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Partly

Is the study design appropriate for the research question?

Partly

Are sufficient details of the methods provided to allow replication by others?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Yes

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Turner syndrome. Other sex chromosome abnormalities. Endocrinology, epidemiology, genetics

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 20 Feb 2019

Jeanne Wolstencroft, UCL Great Ormond Street Institute of Child Health, UK

Dear Claus Gravholt,

Thank you for your comments. We are encouraged to hear that you are convinced of the value of using the PEERS protocol with young women with TS. We have addressed your concerns in turn below:

1.As you correctly point out, there is large variability between young women with TS. Our pilot will only recruit young women experiencing difficulties with friendships who wish to improve their social skills, but within this group there will still be a substantial amount of variability. We are currently conducting a survey of mental health and social skills difficulties in TS (SOAR Study). Our preliminary findings indicate that girls and women with TS have significantly more peer interaction problems when compared to population female norms as measured by the Strengths and Difficulties Questionnaire (Goodman et al., 2010). On our measure of autistic symptomatology (SRS-2; Constantino et al., 2012) 40% of young women with TS scored in the normal range, 14.5% in the mild range, 17.1% in the moderate range and 27.4% in the severely impaired range (SOAR study unpublished findings; n=117). Our sample for the PEERS pilot is representative of this range of social skills difficulties; among our enrolled participants, scores lie in the normal to abnormal range on the Strengths and Difficulties subscale for quality of peer-interactions and they also range from normal to severely impaired on the SRS-2.

We believe it is necessary to conduct a pilot of the PEERS program with young women with TS before conducting a full-scale trial because the program was initially developed to treat adolescent boys with autism. The emerging literature on young women with autism shows clearly that women with social communication impairments face different challenges to those experienced by young men with autistic traits. We will therefore need to adapt the content of the program. For example, some of the lessons focus on issues such as 'good sportsmanship' and 'appropriate uses of humour'; females with TS would not regard these skills as being of core relevance to their social adaptation. Additionally, there is no precedent for delivering social skills training online, therefore there is a need to pilot the acceptability of virtual meeting rooms and to adapt the behavioural rehearsal components of the training to an online environment.

2.You are correct in noting that many girls with TS have impaired adaptation to the social environment that manifests most obviously once they enter adolescence. We have found that

social difficulties emerge and intensify over that period, from the time of entry into secondary education to early adulthood. Therefore, our pilot study's age range (16-20 years) is designed to help young women at a time when their social difficulties are emerging, and they are becoming aware of them.

We are not excluding anyone on the grounds of impaired hearing, if that problem is being successfully managed. Two young women who wear hearing aids are currently enrolled in the pilot study. Unfortunately, the program would need to be substantially modified in order to accommodate those with more profound hearing impairments. The inclusion criteria have been clarified in the protocol v2.

5. As originally devised, the PEERS program required there to be no more than 8-10 participants in the treatment group. The program is very intensive and is characterized by a focus on individual needs as well as on group dynamics. Several staff are required on site to manage the child/parent groups. By adapting the program to be delivered from an online platform we aim to increase its acceptability to participants and to reduce the associated costs. Randomized control trials of PEERS have reported attrition rates of 7-13% (Schohl et al., 2014; Laugeson et al., 2015), hence our prediction that 1-2 participants out of 10 may drop out. However, we are now three-quarters of the way through the pilot trial and we have not yet had any dropouts.

Best wishes,
Jeanne Wolstencroft

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Competing Interests: N/A

Referee Report 27 December 2018

<https://doi.org/10.5256/f1000research.16884.r41256>



David E. Sandberg 

Department of Pediatrics, Medical School, University of Michigan, Ann Arbor, MI, USA

The study protocol describes a pilot project that examines the effectiveness of a social skills training program – originally developed for youth on the autism syndrome spectrum – applied to the social skills deficits of adolescent and young women with Turner syndrome (TS)(45,X). The neurocognitive profile of girls and women with TS has been extremely well documented and has repeatedly been shown to be associated with deficits in social cognition and skills. This aspect of the TS phenotype is likely a significant factor accounting for the gap between educational attainment in this population (shown to exceed to population norms), and their occupational status and measures of independence from family caregivers. Women with TS have also been shown to exhibit both delays and arrest in psychosexual milestones which are more than likely linked to the characteristic social behaviour phenotype associated with this karyotype¹.

The investigators should be commended for proposing to adopt a proven efficacious and effective intervention for social skills deficits to potentially modify the behavioural phenotype in TS. The PEERS program is well-suited to the task because of the similarities in social skills deficits in high-functioning ASD and TS. Work on this topic is long overdue.

The rationale for the pilot study is well described, although the authors have possibly overstated, in the Introduction, the lack of “systematic evaluations of the mental health of young women with TS...”. In fact, there are multiple studies assessing both the psychiatric status and psychosocial/sexual adaptation of this population. What has been sorely missing are psychosocial interventions to potentially ameliorate deficits, and the proposed study is directed precisely toward this objective.

There are the following elements I found missing from the protocol or require further consideration:

1. p.2 Study Design - it's unclear what the following refers to: “All participants will be matched for age, degree of social impairment, intellectual ability and hormone therapy treatment.” Each participant will serve as their own control, so I don't understand the “matching” piece.
2. p. 2. Participant inclusion and exclusion criteria – details are not provided regarding the SOAR questionnaire screening for eligibility based on social skills deficits.
3. Will recruitment be restricted to girls/women with a 45,X karyotype or will those with a variant, including chromosomal mosaicism, be eligible?
4. The Discussion notes that self and parent reports are prone to bias because of expectations regarding the intervention and note that a remedy to overestimating the benefits can come from employing external observers. The investigators justify not employing external observers because of the small scale of this project. However, one could turn that argument around by questioning whether it would be worthwhile to pursue a full-scale trial of PEERS in TS if the effects observed in the pilot are driven by biased reports.

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Is the rationale for, and objectives of, the study clearly described?

Yes

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am a pediatric psychologist involved in clinical care and research focusing on people born with disorders/differences of sex development (DSD): TS is classified as a “sex chromosome DSD”. I served as co-lead for the neurocognition and behaviour section of the updated 2017 clinical practice guidelines for DSD the investigators refer to in the Introduction to their proposal. I have been funded by the US National Institutes of Health for methods development and intervention studies in the area of DSD. I was also a member of the writing group for the Consensus Statement on DSD.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 20 Feb 2019

Jeanne Wolstencroft, UCL Great Ormond Street Institute of Child Health, UK

Dear David Sandberg,

Thank you for your comments. We are encouraged to hear that you are convinced of the value of using the PEERS protocol with young women with TS. We have addressed your concerns in turn below:

1. Participants in the treatment group were chosen because they have similar degrees of social impairment and intellectual ability. We have clarified the wording around the ‘matching of participants’ in the protocol v2. You are correct, they will act as their own controls.

2. Motivation to take part in the intervention is assessed using the PEERS screener interview (Laugeson et al., 2009). It was essential to ensure that the young people and their parents were motivated to take part in the social group in order to minimize potential attrition over the 12 week intervention period. Their social deficits were assessed using a combination of clinical judgement and screening questionnaires:

- Social Aptitude Scale (SAS): The SAS is presented as part of the Development and Wellbeing Assessment's autism module. The SAS is a ten item parent-report measure which assesses social understanding and social ability (as opposed to peer interaction deficits) (Liddle et al., 2008).
- Strengths and Difficulties Questionnaire (SDQ): The SDQ is a brief behavioural screening questionnaire (Goodman et al., 2010). The SDQ includes scales that measure emotional symptoms, conduct problems, hyperactivity/inattention difficulties, peer relationship problems and prosocial behaviour.

3. Recruitment will not be restricted to young women with a monosomic non-mosaic 45,X karyotype. This has now been clarified in the protocol v2.

4. Objectively evaluating the outcome of social skills interventions presents a number of challenges. We agree that expectancy biases are likely to occur. Some outcome measures focus only on self-assessment of social performance or social knowledge. Questionnaires that have been designed for parents, teacher or adult observer respondents, may lack ecological validity. To our knowledge, the outcome of PEERS has not yet been measured by peer-ratings of change. We are currently testing a novel methodology that could address this deficiency.

Currently, we do have some potentially objective measures of change. We obtain teacher ratings of social behaviour, parent reports of changes in the TS girl's social relationships, and individual increases in social knowledge.

As we have indicated, the intervention is designed to take account of individual differences. Accordingly, outcomes are diverse. There will be variability within the sample, and it is unlikely that treatment benefits will be captured by standardized questionnaires alone.

Jeanne Wolstencroft

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Goodman, A., Lamping, D. L., & Ploubidis, G. B. (2010). When to use broader internalising and externalising subscales instead of the hypothesised five subscales on the Strengths and Difficulties Questionnaire (SDQ): data from British parents, teachers and children. *Journal of abnormal child psychology*, 38(8), 1179-1191.

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Competing Interests: N/A

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