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# Tackle your Tics, an intensive tic training: design of a randomised controlled trial

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Tackle your Tics, an intensive tic training: design of a randomised controlled trial

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ABSTRACT

Introduction: This paper outlines the study protocol for the Dutch Tackle your Tics study in youth with tic disorders. Tourette syndrome and chronic tic disorders are prevalent neurodevelopmental disorders, placing considerable burden on youth and their families. Behavioural treatment is the first-line, evidence-based intervention for tic disorders, but tic reduction and utilization rates remain relatively low. Patient associations stress the need for more accessible high-quality treatments, also focusing on improving quality of life. Therefore, the brief, intensive group-based treatment Tackle your Tics was developed. Methods and analysis: Tackle your Tics is a four-day intensive and comprehensive group-based intervention for children and adolescents (9-17 years) with Tourette syndrome or a chronic tic disorder. The programme encompasses exposure and response prevention treatment and additional supporting components (working on adequate coping strategies, relaxation exercises and parent support). To warrant continuation of treatment and the study process despite Covid-19, measures are taken such as switching to online or ‘blended’ sessions in case of quarantine. To study the effectiveness of Tackle your Tics and identify predictors/moderators at baseline, a single-blinded randomised controlled trial (N=104) is conducted, comparing Tackle your Tics (N=52) with a waiting list condition lasting three months (N=52). Assessments are performed at similar time points for both groups: at baseline, after 4 weeks, and at 3- and 6-months follow-up, on tic severity, quality of life, and other psychosocial variables. Ethics and dissemination: Ethics approval has been obtained from the medical ethical committee of the Amsterdam Medical Centre (METC nr NL66340.018.18). Patient representatives are fully integrated as part of the research team. If Tackle your Tics proves to be effective, it can expand evidence-based treatment possibilities for children and adolescents with tic disorders. Identifying the psychosocial predictors/moderators for the effectiveness of this intervention can provide personalised treatment advice in the future. Trial registration: Dutch Trial Registry; NL8052 on 27 September 2019.
INTRODUCTION

Tic disorders, including Tourette Syndrome can seriously impact the quality of life[1][2–5] of children and their families. Tics are sudden, repetitive motor movements or vocalizations which may affect different areas of daily functioning.[3] Many children with tics suffer from poor school functioning[6], emotional/behavioural and social problems[7][8] (e.g. bullying,[9] or stigmatisation[10]). Tics are also associated with family stress and costs for society.[11,12] However, tic severity alone does not determine individual impairment or quality of life[5][13]. In most children tics co-occur with various comorbid disorders and problems, such as attention deficit and hyperactivity[14], compulsions[15], and rage attacks[16], which can be more troublesome than the tics. Although tics disorders are prevalent (0.77-1% for Tourette Syndrome[17,18]), they are still poorly recognised and understood in society.

Efficacy of behavioural treatment for tic reduction is well established and behavioural treatment is considered a first-line intervention for tic disorders.[18] Most research has been done into habit reversal (HRT) and Comprehensive Behavioral Intervention for Tics (CBIT), where the main element is HRT, but exposure and response prevention (ERP) seems promising as well. One comparative study showed no significant difference in tic reduction between ERP and HRT.[19] Research into behavioural treatments for tics has shown moderate to high effect sizes (0.57-1.5), but tic reductions remain relatively low (on average 30% on the Yale Global Tic Severity Scale, YGTSS).[20]

Strengths and limitations of this study:

- This randomised controlled trial studies the effectiveness of the Tackle your Tics programme on tic severity and quality of life of children and their families.
- Identifying predictors/moderators for the effectiveness of this intervention can enhance future personalised treatment advice.
- In this study, an active treatment group is compared with a waiting list control group, that receives the same treatment after three months. No active control condition was compared.
- Patient representatives play an important role in this project, to ensure that the treatment and study process matches the needs and wishes of patients and families.
- Program adjustments and family stress as a result of the Covid-19 pandemic may influence treatment results. This study will provide new insights into possibilities to adjust group programmes during a pandemic.
There are several treatment barriers that keep utilization rates for evidence-based behavioural therapies low.[21][22] Lack of trained therapists may be a barrier for local face-to-face treatment. Consequently, children and their parents must travel to a specialised therapist, which is potentially time-consuming, might cause financial barriers for families with low socio-economic status, and can have impact on the time spent on work, school, and family life. Moreover, the individual therapy and daily ERP home exercises require a lot of motivation and discipline. Strategies to improve homework adherence could optimise treatment outcomes.[23]. Online treatments may be a solution for the lack of local specialised practitioners or limited options for face-to-face contact[24][25], especially during the recent Covid-19 pandemic. Patient associations stress the need for more accessible treatments that focus not only on tic reduction but also on peer and family support on a broader level (daily living issues and problems other than tics), to enhance quality of life of both patients and their families.[26] Positive results have been found for a comprehensive CBIT-programme ‘Living with tics’ that reduced tic-related impairment and improved quality of life in children with tic disorders.[5]

Case studies have suggested that brief, intensive treatment with CBIT[27] and ERP[28] are comparably effective as longer time frame therapies with weekly one hour sessions. In other patient populations (e.g., adolescents with post-traumatic stress disorder, PTSD[29]), obsessive-compulsive disorder (OCD)[30–32], and anxiety disorders[33]), short intensive forms of behavioural treatment have been successful.

In addition, group formats have been shown to be feasible and equally successful as individual therapies for children with tics. Group therapy can offer many benefits such as peer support, reduced waiting lists and increased cost-effectiveness. Outpatient group therapy for children, based on HRT[34,35] or CBIT[36]showed improvements of tic severity and quality of life. Nissen and colleagues found no significant difference in total tic scores of children and adolescents in combined HRT and ERP in a group setting versus in an individual setting.[37] The study of Himle and colleagues (2003) indicated a possible improvement of comorbid symptoms in adolescents after group therapy. Group cognitive behavioural therapy (CBT) for OCD, including ERP, reduced symptoms in participants with tic-related OCD as well as those with non-tic related OCD.[38]

In our previous pilot study (N=14), we demonstrated the feasibility of a brief, intensive and comprehensive group-based exposure therapy programme for children with tic disorders, called Tackle your Tics.[39] Drop-out rates were low (7%), and children and parents rated this form of treatment positively. Parents stated the programme was very helpful. Most parents mentioned their children experienced more control over their tics (85%) or the social contact with other children with tics was helpful (39%). Furthermore, indications of improvements in tic severity as well as quality of life and co-occurring emotional and behavioural problems were found. The mean total tic score (as measured by the YGTSS) decreased with 16% from baseline to follow-up with a medium effect size (p=0.013, effect size=0.412). Quality of life scores improved with 20% from baseline to follow-up (p=0.002,
effect size=0.584). The group format, making use of (co)therapists, offered opportunities to train more behavioural therapists. These pilot findings underlined the urgent need for a larger randomised controlled trial (RCT) to determine the effectiveness of our brief, intensive group-based programme for children with tic disorders. Based on feedback from parents from this pilot study, the following adaptations were applied to the programme: (1) we have added parent sessions, in which parents can learn how to support their child’s home exercises and to (2) and an extra meeting after the fourth day, to motivate the children to continue doing their ERP exercises at home.

The aim of this randomised controlled trial is to test the effects of Tackle your Tics on tic severity, quality of life, premonitory urges, beliefs about tics, daily functioning, family functioning, treatment adherence and satisfaction, and treatment costs from a societal perspective. We will compare results on these outcomes in our intervention group with those in a waiting list control group. Furthermore, we aim to identify baseline psychosocial and medical predictors/moderators for the effectiveness of Tackle your Tics. Exploring which children benefit most from this brief intensive treatment, will offer opportunities to improve personalised treatment advice.

Several baseline characteristics possibly influence differential response to Tackle your Tics based on studies on predictors and moderators of behavioural interventions for tic disorders and other neurodevelopmental disorders. In tic disorders, greater tic severity and positive participant expectancy predict greater tic improvement whereas anxiety disorders and premonitory urge severity predict lower tic reduction.[40] In a meta-analysis of behaviour therapy for Tourette syndrome, co-occurring attention deficit hyperactivity disorder (ADHD), a smaller number of therapy sessions and a mean younger age were predictors of poorer outcome.[20] Homework adherence has been shown to predict tic severity reduction [18]. In a study on predictors and moderators of behavioural intervention for anxiety disorders, higher caregiver strain predicted lower improvement.[41]

METHODS AND ANALYSIS

Design: a multi-centre, single-blinded randomised controlled trial comparing the efficacy of the Tackle your Tics intervention (TyT, N=52) with a waiting list control group (WLCG, N=52) in children and adolescents with tic disorders.

Participants

Inclusion criteria: children and adolescents must meet all of the following criteria: (a) aged 9 to 17 years; (b) diagnosed with Tourette Syndrome or persistent (motor/vocal) tic disorder, using diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition[42]; (c) with at least moderate severity as indicated by a YGTSS total tic score >13 (>9 for children with motor or vocal tics only).
Exclusion criteria: (a) behavioural treatment for tics in the past 12 months; (b) pharmacological treatment for tics or another diagnosed psychiatric disorder that has not been stable the past six weeks or with planned changes during study participation; (c) poor mastery of the Dutch language; (d) IQ < 75; (e) serious physical disease; (f) substance abuse; (g) suicidality; (h) psychotic disorder; (i) poor group functioning and/or low motivation (as reported by child, parents or local therapist). Since Tourette Syndrome is seldom seen without comorbidities[15], co-occurring attention deficit–hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), anxiety disorders or mood disorders are allowed, unless the disorder requires immediate treatment or change in current treatment.

Recruitment and randomisation

From July 2020 to end 2022, children and adolescents are recruited by the Dutch Tourette Association and the participating expert centres on tic disorders in youth: Levvel, Accare and Yulius. After being informed by the therapist and researcher about this study, eligible participants and their parents are asked to sign informed consent forms.

Participants are randomly allocated, using block randomisation, and stratified by gender, by an independent researcher to either the brief, intensive TyT condition or the WLCG condition. The size of the blocks (2-4 patients) is randomly selected and is unknown to the researchers, to avoid allocation predictability. For each block, 50% the patients will be allocated to Tackle your Tics and 50% to the waiting list group. The randomization process is performed using a computerized data management system (Castor EDC). Patients and families are specifically instructed not to tell their condition to the researcher performing the assessments.

Patients in the TyT condition (N=52) will receive the Tackle your Tics intervention one month after randomisation, in groups of approximately 4-8 patients per group, while patients in the WLCG condition (N=52) receive this same intervention after a waiting period of 3 months (total sample: N = 104). Treatment for all participants takes place at Levvel, Amsterdam.

Therapists and patient representatives

The Tackle your Tics programme is provided by experienced therapists from three participating centres with expertise on tic disorders in the Netherlands: Levvel (Amsterdam), Accare (Groningen) and Yulius (Dordrecht) together with patient representatives from the national patient organisation (Stichting Gilles de la Tourette). Therapists are academically trained (clinical) psychologists or cognitive behavioural therapists, with 3-15 years of experience in treating tic disorders. Co-therapists from these sites are trained during the treatment, and have the same academical background, with less (0-3 years of) experience in treating tic disorders. Depending on group size (4-8 participants), a team of 2-3 experienced therapists, 1-2 co-therapists, and 1-2 trained patient representatives will provide the treatment programme. All team members are blinded for treatment allocation of the participants.
**Intervention**

Behavioural therapy intervenes in the sequence of negative reinforcement between premonitory sensations or ‘tic alarms’, the subsequent tics and decrease of the sensation. In ERP, patients with tic disorders learn to suppress their tics for prolonged time (response prevention), while the focus remains on these sensations (exposure). This allows the patient to learn to tolerate these sensations or ‘tic alarms’, resulting in a reduction of tics[43][19]. The therapist coaches and encourages the patient to improve time records, and provokes the tic alarms to optimise exposure, e.g., by attending the sensations, playing exciting games or talking about tics.

*Tackle your Tics* offers the same number of ERP therapy hours as regular, 12 weekly individual ERP-sessions, but in a shorter period. The brief, intensive group programme covers three consecutive days and one booster day one week later, followed by a ‘get together afternoon’ after one month. The programme days consist of ERP-sessions and several supporting, relaxing, and motivating components, to enhance motivation and homework adherence, and reduce drop out (see Table 1).

**ERP-sessions**

One hour treatment sessions with ERP are offered in small subgroups of 2 or 3 children. Participants assist each other by timing and registering their tics and encourage each other to enhance motivation and peer support. When needed, participants can train a specific tic reduction individually with a therapist in one of the sessions. To generalise learned skills, from about day 3 the therapist can expand the exercises to outdoors or other situations (e.g., playing an exciting game, riding a bike), depending on the individual progress of the participants.

**Coping strategy workshops**

According to a large European patient survey[26] patients need support that does not focus on tics only but also on other symptoms and problems related to tic disorders and daily living issues (dealing with Tourette Syndrome at home, work and school). Therefore, as advised by the Dutch national patient association, young adult patients offer one hour coping strategy workshops each programme day. They teach the children how to cope with their symptoms in a positive, creative way. In the workshops three themes are discussed and visualized (by writing, painting and mind mapping): self-acceptance, solution-oriented thinking and positive characteristics and strengths.

**BT-Coach**

A training app, *BT-Coach*, is used to motivate the children to continue with the exercises at home and enhance homework adherence.[44] In the absence of a therapist, the app takes over the coaching role during homework exercises. An audio-voice stimulates the child to suppress all tics, endure accompanying sensations, and beat ? suppression time records. After having a tic, the participant clicks on a button ‘Tap for a Tic’ to register non-suppressed tics. BT-Coach stimulates the child to
stop the next tic and work on new records. Usage of the app is also included in a relapse prevention plan (‘keep the tics away plan’) that participants work on during the third and fourth training day.

Parent involvement
Parents are involved in the treatment by (a) parent meetings, (b) attending one therapy session to learn to coach their child during exercises and (c) participating in feedback sessions at the end of all treatment days, to evaluate and answer questions. In three parent meetings of 60 or 120 minutes (see table 1), therapists offer psychoeducation to parents, discuss expectations and how parents can help their child at home during and after treatment. Trained patient representatives accompany the meetings to exchange experiences in the parent group and offer emotional support.

Psycho-education
A small workbook, partly based on ‘Tics - workbook for children’ by Verdellen, van de Griendt and Kriens[45] has been developed specifically for this programme, to teach children and adolescents about premonitory sensations (‘tic alarms’), tic triggers, difficult moments and practicing at home. Daily psycho-education classes of 60 minutes are given jointly by therapists and patient representatives in which clinical and experiential knowledge complement each other.

Relaxation
The programme contains short (15 minutes) commonly used relaxation exercises, focusing on breathing and muscle relaxation techniques.

Covid-19 adjustments
Due to Covid-19 regulations, the first treatment groups were postponed to September 2020. The treatment programme had to be adapted according to the national pandemic regulations. We distinguish four variants of the programme: (1) the original face-to-face programme, (2) a slightly modified programme with online parent meetings and some basic safety measures (e.g., health check), (3) a ‘blended’ programme, a mix of face-to-face and online participation, in case some participants or team members cannot complete the programme face-to-face (e.g., due to quarantine), and (4) a completely online programme, if face-to-face treatment is not possible at all due to national policies (see Table 2).

Training and treatment integrity
Therapists of participating centres are trained in intensive ERP for tic disorders by a leading Dutch expert. Two adult experts by experience developed the coping strategy workshops and will train other patient representatives. A standardised training programme for therapists and patient representatives (with online training videos, a PowerPoint presentation, and a detailed program script) is used. To enhance treatment integrity, team intervision meetings for every new treatment group are conducted. Treatment integrity is assessed by two independent, trained raters, rating a random 20% of
all programme sessions (10% TyT and WLCG condition 10%). Sessions will be audiotaped, after having received consent from patients and parents.

**Outcome measures**

At four moments, at similar time intervals for both the TyT and WLCG condition, assessments will be done pre- and post-treatment, and at 3- and 6-months follow-up, using validated, psychometrically sound instruments, with both patients, parents, and teachers as informants. See Figure 1 for the study procedure.

The researcher psychologist (MSc) performing the assessments will be blinded to the group conditions. Parents and patients are explicitly instructed not to communicate their group condition to the researcher. Self-report questionnaires are completed online by patients and parents. One questionnaire (Outcome Rating Scales and Session Rating scales, ORS/SRS[46]) is completed by the participants during the treatment days.

**Primary outcome**

*Tic severity* (key outcome) will be measured by the YGTSS[47], a commonly used, reliable and valid semi-structured interview for the assessment of tic severity.[48] The global tic severity score (response range 0-100) is composed of an impairment score (0-50) and a total tic score (0-50). The total tic score, the summation of the motor tic score (0-25) and the total vocal tic score (0-25), is the primary outcome measure. A high score indicates a high severity of the tics regarding number, frequency, intensity, complexity and/or interference. At T2, directly post intervention as our primary end point, we define a 25% reduction of this score as a positive response.[49]

**Secondary outcomes**

*Quality of life* is measured by the Gilles de la Tourette Syndrome Quality of Life Scale for children and adolescents; C&A-GTS-QOL[50], a 27-item patient-reported scale for the measurement of health related quality of life in patients with Tourette Syndrome (range 27-135), with high internal consistency and test-retest reliability. A high score indicates more problems in daily life and a lower quality of life.

Other secondary outcome measures are: tic-related cognitions, emotional and behavioural functioning, social competence, school functioning, self esteem, family functioning, treatment satisfaction, quality of life related to cost effectivity, and cost-effectiveness/medical consumption. For the instruments used and their psychometric characteristics, see Table 3.

**Moderators and predictors**

To identify possible baseline psychosocial moderators and predictors for the effectiveness of *Tackle your Tics* the following variables are studied for moderation and prediction: tic severity, premonitory
urge severity, age, gender, family functioning, homework adherence and comorbidity (for the instruments used, see Table 3).

**Patient characteristics**

Demographic data are derived by the researcher from the medical files and a semi-structured interview about possible comorbid problems (Anxiety Disorder Interview Schedule; ADIS, both parent and child version (>12 years).[51] Demographical data encompass e.g., sex, gender, age in years/months, school class of child, cultural background, parental age and their marital, educational, and socio-economic status, according to the International Standard Classification of Occupations (ISCO-08)[52], psychiatric comorbidities, previous treatment of tics (behavioural therapy or medication) and outcomes thereof, family history of tics and autoimmune diseases in 1st and 2nd family relatives.

**Sample size calculation**

To determine the effects on the primary outcome (total tic score as measured by the YGTSS), at the primary endpoint (T2), at an effect size of Cohen’s d=0.5 (according to Cohen, 1988), with a power of 0.8, a sample size of 52 patients per group (N=104) is needed to detect univariate differences (p<0.05) between the TYT and WLCG group. In addition, we will test the background characteristics of participants versus patients who refused to participate, to determine whether there is selection bias. Based on this sample size calculation, the intervention group will encompass approximately 7-8 groups of approximately 4-8 patients with tics disorders.

Based on our clinical experiences and the percentage of dropouts in the feasibility study (7%), we aim to include and randomise at least 112 patients, to achieve the total sample size of 104, necessary to answer our research questions.

**Statistical analysis**

To check for selection bias, differences in patient characteristics between participants and non-participants (no informed consent) will be tested by independent t-tests, Chi-square tests, and Fisher’s exact tests, where appropriate. In the same way, differences in baseline characteristics will be tested between the TyT and WLCG condition.

To test the effectiveness of Tackle your Tics, group differences between the TyT brief intensive therapy versus WLCG will be analysed using the intention-to-treat-principle. Changes on the key outcome tic severity will be corrected for group effect and analysed with Generalised Estimating Equations (GEE).

Based on the pilot study results, changes in tic severity are expected between pre (T1) and post (T2) treatment, as well as further improvement at 12 weeks (T3) and 6 months (T4) follow up. Group mean differences at the four measurements (T1-T2-T3-T4) will be tested using GEE, to show outcomes on tic severity, quality of life, premonitory urges, beliefs about tics, daily functioning:
emotional/behavioural, social, and school functioning, self esteem, family functioning (including
caregiver strain), treatment alliance/ satisfaction, and cost effectivity.

To check for possible effects of the programme adjustments to Covid-19 measures (see Table 2),
the differences in outcomes between the (original or slightly adapted) face-to-face groups and the
blended/online groups will be analysed with GEE, as well as the differences between the results of the
total study population and the study population without the participants of blended or online groups, to
see if there are differences in the effects.

ETHICS AND DISSEMINATION

Ethics approval
This study is performed in accordance with the Declaration of Helsinki and approved by the medical
ethical committee of the Amsterdam Medical Centre (METC nr NL66340.018.18). Representatives of
the Dutch patient organisation are active members of the research team and continuously review the
research process from the patients’ perspective.

Informed consent
Oral and written information is given to parents and patients, and written consent from patients over
12 years and parents is received.

Patient and public involvement
Patient representatives are ‘experts by experience’ and play a unique and important role in this project
and are equal partners in the research team from start to finish. Next to the programme contributions
already mentioned, their contributions include co-designing the study, obtaining grants, recruitment,
collection and interpretation of the data, co-writing publications, and giving congress presentations.
This active involvement from the patient’s perspective ensures that the research process matches the
needs and wishes of patients and families.

Dissemination
Results of the study will be presented on national and international conferences, peer reviewed
scientific journals, patient organisation meetings and public media. If Tackle your Tics proves to be
effective, the programme will be implemented in centres for youth mental health care.

DISCUSSION
This study is, to our knowledge, the first randomised controlled trial studying the effectiveness of a
brief, intensive group-based exposure therapy for children and adolescents with chronic tic disorders.
If this brief, intensive ERP treatment is shown to be effective, it can offer several benefits.
Programmes like *Tackle your Tics* can expand the access to behavioural treatment for youth living in different areas, where specialised therapists trained in treatment of tics are unavailable. Families may find it more feasible to follow a brief, compromised treatment in four days with earlier benefit of possible treatment results and additional support. The programme also offers opportunities to educate behavioural therapists in behavioural (group) therapy for tics. This study will show which children benefit most from an intensive group-based format, which will make it easier for practitioners to give personalised treatment advice. A possible limitation could be that the active treatment condition is compared with a waiting list condition. No active control condition was compared, although the participants in the waiting list condition received the same treatment after three months. Since the last follow-up measurement is conducted six months after treatment, it is unclear what the effectiveness will be in the longer term. Effects of programme adjustments and family stress as a result of the Covid-19 pandemic will provide new insights into the feasibility to adjust group programmes during changing situations and the influence on treatment results.

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**Authors’ contributions**

APH, CH, CWJV, JMTMG, LPLB, KJK, DC, PJH, and EMWJU contributed to the design of the study. APH drafted the article. All authors revised the article critically and approved the final version.

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**Conflicts of interest**

CWJV and JMTMG developed and published the manual ‘Tics’ and the training app BT-Coach (BT-Tics Foundation), which are both being used in the programme. On behalf of all authors, the corresponding author states that there are no other conflicts of interest.
Tables and figures

Figure 1: Flowchart study procedure *Tackle your Tics*
Table 1: *Tackle your Tics* therapy programme for children and adolescents

Three parallel parent meetings are organised on day 1 and day 4 (10:00-12:00) and on the ‘get together afternoon’ (15:45-16:45). Psychoeducation and workshops are offered in subgroups of 3-5 children, parallel to the ERP sessions of the other participants (except for small groups that consist of 4 or 5 children).

| Day 1 | Day 2 | Day 3 | Day 4 booster day (after 1 week) | Get together afternoon (after 1 month) |
|-------|-------|-------|----------------------------------|---------------------------------------|
| 9:30-10:00 | Welcome and acquaintance game (all participants and parents) | | | |
| 10:00-11:00 | Psychoeducation or therapy session (subgroups) | Psychoeducation or therapy session (subgroups) | Psychoeducation or therapy session (subgroups) | Psychoeducation or therapy session (subgroups) |
| 11:00-11:10 | Short break (all participants) | Short break (all participants) | Short break (all participants) | Short break (all participants) |
| 11:10-12:10 | Psychoeducation or therapy session (subgroups) | Psychoeducation or therapy session (subgroups) | Psychoeducation or therapy session (subgroups) | Psychoeducation or therapy session (subgroups) |
| 12:10-12:40 | Lunch break (all participants) | Lunch break (all participants) | Lunch break (all participants) | Lunch break (all participants) |
| 12:40-13:40 | Workshop coping strategies or therapy session (subgroups) | Workshop coping strategies or therapy session (subgroups) | Workshop coping strategies or therapy session (subgroups) | Workshop coping strategies or therapy session (subgroups) |
| 13:40-14:10 | Playtime (all participants) | Playtime (all participants) | Playtime (all participants) | Playtime (all participants) |
| 14:10-15:10 | Workshop coping strategies or therapy session (subgroups) | Workshop coping strategies or therapy session (subgroups) | Workshop coping strategies or therapy session (subgroups) | Workshop coping strategies or therapy session (subgroups) |
| 15:10-15:25 | Relaxation therapy (all participants) | Relaxation therapy (all participants) | Relaxation therapy (all participants) | Relaxation therapy (all participants) |
| 15:25-15:40 | group therapy session (all participants) | group therapy session (all participants) | group therapy session (all participants) | group therapy session (all participants) |
| 15:40-15:55 | Short evaluation (all participants) | Short evaluation (all participants) | Short evaluation (all participants) | Short evaluation (all participants) |
| 14:00-14:30 | Get together (participants and parents): welcome | | | |
| 14:30-15:30 | Evaluation (participants and parents) | | | |
| 15:30-15:45 | Break | | | |
| 15:45-16:45 | Workshop (all participants) | | | |
| Time          | Activity                                                                 |
|--------------|---------------------------------------------------------------------------|
| 15:55-16:30  | Feedback: therapist with parents and participant                          |
|              | Feedback: therapist with parents and participant                          |
|              | Feedback: therapist with parents and participant                          |
|              | Feedback: therapist with parents and participant                          |
| 16:45-17:00  | Get together (participants and parents): closing                           |

**Table 2: Adjustments to Covid-19 measures on the *Tackle your Tics* programme**

| Indications                                                                 | Original programme (see table 1) | Adapted programme                                                                 | Blended programme                                                                 | Online programme                                                                 |
|---------------------------------------------------------------------------|---------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| If no Covid-19 regulations are applicable                                 | Face-to-face                     | Face-to-face, with adjustments based on national Covid-19 regulations, e.g.: health check, protective equipment, larger spaces, ventilation | Mix of face-to-face with Covid-19 adjustments and online participation            | Completely online, in shortened form                                          |
| In case of applicable Covid-19 regulations                                 |                                  |                                                                                    |                                                                                  |                                                                                  |
| If some participants or team members cannot continue participation after a face-to-face start, e.g.: due to quarantine or positive test |                                  |                                                                                    |                                                                                  |                                                                                  |
| If face-to-face group treatment is impossible from the start due to policy changes |                                  |                                                                                    |                                                                                  |                                                                                  |

**Programme elements for participants**

- Face-to-face
- Face-to-face, with adjustments based on national Covid-19 regulations, e.g.: health check, protective equipment, larger spaces, ventilation
- Mix of face-to-face with Covid-19 adjustments and online participation
- Completely online, in shortened form

**Programme elements for parents**

- Face-to-face parent meetings in parallel during the children’s programme, face-to-face parent sessions and feedback sessions with the therapist
- Online parent meetings in the evenings, face-to-face parent sessions and feedback sessions with the therapist
- Online parent meetings in the evenings, face-to-face or online parent sessions and feedback sessions with the therapist
- Online parent meetings in the evenings, online parent sessions and feedback sessions with the therapist
Table 3: Assessment plan for the Tackle your Tics study (N=104) at four assessment moments (N=104)

| Variable                          | Questionnaire                                      | Items | Score range       | Score indication                                      | Assessment moments |
|-----------------------------------|----------------------------------------------------|-------|-------------------|-------------------------------------------------------|--------------------|
| **Primary outcome**               |                                                    |       |                   |                                                       |                    |
| Tic severity*                     | Yale Global Tic Severity Scale (YGTSS) [47]        | 11    | 0-100             | Low-high tic severity                                  | R                  |
|                                   |                                                    |       |                   |                                                       | R                  |
|                                   |                                                    |       |                   |                                                       | R                  |
|                                   |                                                    |       |                   |                                                       | R                  |
| **Secondary outcomes**            |                                                    |       |                   |                                                       |                    |
| Quality of life                   | Gilles de la Tourette Syndrome Quality of Life Scale for children and adolescents (C&A-GTS-QOL) [50] | 27    | 27-135, scale scores | Low-high degree of problems in daily life (= high-low quality of life) | C                  |
|                                   |                                                    |       |                   |                                                       | C                  |
|                                   |                                                    |       |                   |                                                       | C                  |
|                                   |                                                    |       |                   |                                                       | C                  |
| Tic-related cognitions           | Beliefs about Tics Scale (BATS) [53] (Dutch translation) | 20    | 20-80             | Low-high degree of tic-related cognitions             | C                  |
|                                   |                                                    |       |                   |                                                       | C                  |
|                                   |                                                    |       |                   |                                                       | C                  |
| Emotional/behavioural functioning | Child Behavior Checklist (CBCL-18) [54,55]        | 112   | 0-220             | Low-high degree of emotional and behavioural problems | P                  |
|                                   |                                                    |       |                   |                                                       | P                  |
|                                   |                                                    |       |                   |                                                       | P                  |
| Emotional/behavioural functioning | Youth-Self Report (11y and older) (YSR) [55]      | 112   | 0-220             | Low-high degree of emotional and behavioural problems | C                  |
|                                   |                                                    |       |                   |                                                       | C                  |
| School functioning                | Teacher Report form (TRF) [55]                     | 112   | 0-220             | Low-high degree of emotional and behavioural problems | T                  |
|                                   |                                                    |       |                   |                                                       | T                  |
| Self esteem                       | Self Perception Profile for Children [56] (Dutch versions for children or adolescents: CBSK, CBSA) [57] | 36    | scale scores      | Low-high experience of competence and self esteem      | C                  |
|                                   |                                                    |       |                   |                                                       | C                  |
| Quality of life related to health | EQ-5D /EQ-5D-Y [58–60]                            | 5     | 1-5 per item      | Low-high health related quality of life                | C,P               |
|                                   |                                                    |       |                   |                                                       | C,P               |
|                                   |                                                    |       |                   |                                                       | C,P               |
| Stress of parenting               | Stress of parenting questionnaire (OBVL) [61]      | 34    | 34-136            | Low-high stress of parenting                           | P                  |
|                                   |                                                    |       |                   |                                                       | P                  |
|                                   |                                                    |       |                   |                                                       | P                  |
| Care-related quality of life in informal caregivers (parents) | Care Related Quality of Life (CarerQol) [62] | 7     | 0-100             | Low-high burden of providing informal care             | P                  |
|                                   |                                                    |       |                   |                                                       | P                  |
|                                   |                                                    |       |                   |                                                       | P                  |
| Cost-effectiveness/medica l consumption | Treatment Inventory of Costs in Patients with psychiatric disorders (TIC-P) /TIC-P-Y [63] | 57    |                   | Low-high medical costs and productivity losses         | C,P               |
|                                   |                                                    |       |                   |                                                       | C,P               |
|                                   |                                                    |       |                   |                                                       | C,P               |
| Treatment satisfaction/burden/homework adherence | Treatment satisfaction forms, developed for this study (child/parent version) | 17 (C) | 11-55             | Low high treatment satisfaction                        | C,P               |
|                                   |                                                    |       |                   |                                                       | C,P               |
|                                   |                                                    |       |                   |                                                       | C,P               |
| Moderator/predictor variables | Therapeutic alliance, patient functioning | Outcome Rating Scales and Session Rating scales (during treatment, child/youth version) | 8 | 0-40 per scale | Low-high |

**Demographic data**

- Sex, gender, age

**Family functioning**

- Family Assessment Device (general functioning subscale)

**Psychiatric comorbidities**

- Anxiety Disorders Interview Schedule

**Premonitory urges**

- Premonitory Urges for Tics Scale

Abbreviations: P=parent report, C=child report, T=teacher report, R=researcher/clinician report

*Tic severity at baseline and homework adherence will also be included in the moderator/predictor analyses (see Methods and Analysis)
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CONSORT 2010 checklist of information to include when reporting a randomised trial*

| Section/Topic   | Item No | Checklist item                                                                 | Reported on page No |
|-----------------|---------|---------------------------------------------------------------------------------|---------------------|
| Title and abstract | 1a      | Identification as a randomised trial in the title                              | 1                   |
|                 | 1b      | Structured summary of trial design, methods, results, and conclusions (specific guidance see CONSORT for abstracts) | 2                   |
| Introduction    | 2a      | Scientific background and explanation of rationale                             | 3-5                 |
|                 | 2b      | Specific objectives or hypotheses                                               | 5                   |
| Methods         | 3a      | Description of trial design (such as parallel, factorial) including allocation ratio | 5                   |
|                 | 3b      | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | n.a.                |
| Participants    | 4a      | Eligibility criteria for participants                                           | 5-6                 |
|                 | 4b      | Settings and locations where the data were collected                           | 7-9                 |
| Interventions   | 5       | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 7-8                 |
| Outcomes        | 6a      | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 9-10                |
|                 | 6b      | Any changes to trial outcomes after the trial commenced, with reasons          | n.a.                |
| Sample size     | 7a      | How sample size was determined                                                  | 10                  |
|                 | 7b      | When applicable, explanation of any interim analyses and stopping guidelines    | n.a.                |
| Randomisation:  | 8a      | Method used to generate the random allocation sequence                          | 6                   |
| Sequence        | 8b      | Type of randomisation; details of any restriction (such as blocking and block size) | 6                   |
| Allocation      | 9       | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | 6, 9                |
| concealment     | mechanism |                                                                                  |                     |
| Implementation  | 10      | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | 6                   |
| Blinding        | 11a     | If done, who was blinded after assignment to interventions (for example, participants, care providers, those | 6, 9                |
| 1. | 2. | 3. | 4. | 5. | 6. | 7. | 8. | 9. | 10. | 11. | 12. | 13. | 14. | 15. | 16. | 17. | 18. | 19. | 20. | 21. | 22. | 23. | 24. | 25. |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| **Statistical methods** | 11b | If relevant, description of the similarity of interventions | 3, 12 |
| | 12a | Statistical methods used to compare groups for primary and secondary outcomes | 10-11 |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | 10-11 |
| **Results** | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | n.a. (protocol) |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | n.a. (protocol) |
| **Recruitment** | 14a | Dates defining the periods of recruitment and follow-up | 6, 9 |
| | 14b | Why the trial ended or was stopped | n.a. (protocol) |
| **Baseline data** | 15 | A table showing baseline demographic and clinical characteristics for each group | n.a. (protocol) |
| **Numbers analysed** | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | n.a. (protocol) |
| **Outcomes and estimation** | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | n.a. (protocol) |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | n.a. (protocol) |
| **Ancillary analyses** | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | n.a. (protocol) |
| **Harms** | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | n.a. (protocol) |
| **Discussion** | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | 11-12 |
| **Generalisability** | 21 | Generalisability (external validity, applicability) of the trial findings | n.a. (protocol) |
| **Interpretation** | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | n.a. (protocol) |
| **Other information** | 23 | Registration number and name of trial registry | 2 |
| | 24 | Where the full trial protocol can be accessed, if available | 2 |
| | 25 | Sources of funding and other support (such as supply of drugs), role of funders | 12 |

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).
Effectiveness of ‘Tackle your Tics’, a brief, intensive group-based exposure therapy programme for children with tic disorders: study protocol of a randomised controlled trial

| Journal: | *BMJ Open* |
|-----------|-----------|
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STUDY PROTOCOL

Effectiveness of ‘Tackle your Tics’, a brief, intensive group-based exposure therapy programme for children with tic disorders: study protocol of a randomised controlled trial

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ABSTRACT

Introduction: This paper outlines the study protocol for the Dutch Tackle your Tics study in youth with tic disorders. Tourette syndrome and chronic tic disorders are prevalent neurodevelopmental disorders, placing considerable burden on youth and their families. Behavioural treatment is the first-line, evidence-based intervention for tic disorders, but tic reduction and utilization rates remain relatively low. Patient associations stress the need for more accessible high-quality treatments, also focusing on improving quality of life. Therefore, the brief, intensive group-based treatment Tackle your Tics was developed. Methods and analysis: Tackle your Tics is a four-day intensive and comprehensive group-based intervention for children and adolescents (9-17 years) with Tourette syndrome or a chronic tic disorder. The programme encompasses exposure and response prevention treatment and additional supporting components (coping strategies, relaxation exercises and parent support). To study the effectiveness of Tackle your Tics and identify predictors/moderators at baseline, a single-blinded randomised controlled trial (N=104) is conducted, comparing Tackle your Tics (N=52) with a waiting list condition lasting three months (N=52). Assessments are performed at similar time points for both groups: at baseline, after 4 weeks, and at 3- and 6-months follow-up, on tic severity, quality of life, and other psychosocial variables. Ethics and dissemination: Ethics approval has been obtained from the medical ethical committee of the Amsterdam Medical Centre (METC nr NL66340.018.18, v3 June 2020). Findings will be presented on national and international conferences, peer reviewed scientific journals, patient organisation meetings and public media. Patient representatives are fully integrated as part of the research team. If Tackle your Tics proves to be effective, it can expand evidence-based treatment possibilities for children and adolescents with tic disorders. Identifying the psychosocial predictors/moderators for the effectiveness of this intervention can provide personalised treatment advice in the future. Trial registration: Dutch Trial Registry; NL8052 on 27 September 2019.
INTRODUCTION

Tic disorders, including Tourette Syndrome can seriously impact the quality of life[1][2–5] of children and their families. Tics are sudden, repetitive motor movements or vocalizations which may affect different areas of daily functioning.[3] Many children with tics suffer from poor school functioning[6], emotional/behavioural and social problems[7][8] (e.g. bullying,[9] or stigmatisation[10]). Tics are also associated with family stress and costs for society.[11,12] However, tic severity alone does not determine individual impairment or quality of life[5][13]. In most children tics co-occur with various comorbid disorders and problems, such as attention deficit and hyperactivity[14], compulsions[15], and rage attacks[16], which can be more troublesome than the tics. Although tics disorders are

Strengths and limitations of this study:

- This study uses a randomised controlled design, with a large sample size, in which workshops given by trained ‘experts by experience’ are an integral part of the treatment protocol.

- Longitudinal assessments are performed at pre and post treatment, but also at longer term follow-up (after 6 months), using a multi-informant approach (children, parents, therapists) and psychometrically sound assessment instruments, also studying possible predictors and moderators of treatment outcomes.

- In this study, no active control condition is being compared, which limits interpretation of the results.

- Program adjustments and family stress as a result of the Covid-19 pandemic may influence treatment results.
prevalent (0.77-1% for Tourette Syndrome[17,18]), they are still poorly recognised and understood in society.

Efficacy of behavioural treatment for tic reduction is well established and behavioural treatment is considered a first-line intervention for tic disorders.[18] Most research has been done into habit reversal (HRT) and Comprehensive Behavioral Intervention for Tics (CBIT), where the main element is HRT, but exposure and response prevention (ERP) seems promising as well. One comparative study showed no significant difference in tic reduction between ERP and HRT.[19] Research into behavioural treatments for tics has shown moderate to high effect sizes (0.57-1.5), but tic reductions remain relatively low (on average 30% on the Yale Global Tic Severity Scale, YGTSS).[20]

There are several treatment barriers that keep utilization rates for evidence-based behavioural therapies low.[21][22] Lack of trained therapists may be a barrier for local face-to-face treatment. Consequently, children and their parents must travel to a specialised therapist, which is potentially time-consuming, might cause financial barriers for families with low socio-economic status, and can have impact on the time spent on work, school, and family life. Moreover, the individual therapy and daily ERP home exercises require a lot of motivation and discipline. Strategies to improve homework adherence could optimise treatment outcomes.[23] Online treatments may be a solution for the lack of local specialised practitioners or limited options for face-to-face contact[24][25], especially during the recent Covid-19 pandemic. Patient associations stress the need for more accessible treatments that focus not only on tic reduction but also on peer and family support on a broader level (daily living issues and problems other than tics), to enhance quality of life of both patients and their families.[26] Positive results have been found for a comprehensive CBIT-programme ‘Living with tics’ that reduced tic-related impairment and improved quality of life in children with tic disorders.[5]

Case studies have suggested that brief, intensive treatment with CBIT[27] and ERP[28] are comparably effective as longer time frame therapies with weekly one hour sessions. In other patient populations (e.g., adolescents with post-traumatic stress disorder, PTSD[29]), obsessive-compulsive disorder (OCD)[30–32], and anxiety disorders[33]), short intensive forms of behavioural treatment have been successful.

In addition, group formats have been shown to be feasible and equally successful as individual therapies for children with tics. Group therapy can offer many benefits such as peer support, reduced waiting lists and increased cost-effectiveness. Outpatient group therapy for children, based on HRT[34,35] or CBIT[36] showed improvements of tic severity and quality of life. Nissen and colleagues found no significant difference in total tic scores of children and adolescents in combined HRT and ERP in a group setting versus in an individual setting.[37] The study of Himle and colleagues (2003) indicated a possible improvement of comorbid symptoms in adolescents after group therapy. Group cognitive behavioural therapy (CBT) for OCD, including ERP, reduced symptoms in participants with tic-related OCD as well as those with non-tic related OCD.[38]
In our previous pilot study (N=14), we demonstrated the feasibility of a brief, intensive and comprehensive group-based exposure therapy programme for children with tic disorders, called Tackle your Tics.[39] Drop-out rates were low (7%), one out of a total of 14 participants dropped out due to poor group functioning, which was not identified during intake. The other participants completed the full therapy program. Parents stated the programme was very helpful. Most parents mentioned their children experienced more control over their tics (85%) or the social contact with other children with tics was helpful (39%). Furthermore, indications of improvements in tic severity as well as quality of life and co-occurring emotional and behavioural problems were found. The mean total tic score (as measured by the YGTSS) decreased with 16% from baseline to follow-up with a medium effect size (p=0.013, effect size=0.412). Quality of life scores improved with 20% from baseline to follow-up (p=0.002, effect size=0.584). The group format, making use of (co)therapists, offered opportunities to train more behavioural therapists. These pilot findings underlined the urgent need for a larger randomised controlled trial (RCT) to determine the effectiveness of our brief, intensive group-based programme for children with tic disorders. Based on feedback of parents from this pilot study, the following adaptations were applied to the programme: (1) we have added parent sessions, in which parents can learn how to support their child’s home exercises and to (2) and an extra meeting after the fourth day, to motivate the children to continue doing their ERP exercises at home.

The aim of this randomised controlled trial is to test the effects of Tackle your Tics on tic severity, quality of life, premonitory urges, beliefs about tics, daily functioning, family functioning, treatment adherence and satisfaction, and treatment costs from a societal perspective. We will compare results on these outcomes in our intervention group with those in a waiting list control group. Furthermore, we aim to identify baseline psychosocial and medical predictors/moderators for the effectiveness of Tackle your Tics. Exploring which children benefit most from this brief intensive treatment, will offer opportunities to improve personalised treatment advice.

Several baseline characteristics possibly influence differential response to Tackle your Tics based on studies on predictors and moderators of behavioural interventions for tic disorders and other neurodevelopmental disorders. In tic disorders, greater tic severity and positive participant expectancy predict greater tic improvement whereas anxiety disorders and premonitory urge severity predict lower tic reduction.[40] In a meta-analysis of behaviour therapy for Tourette syndrome, co-occurring attention deficit hyperactivity disorder (ADHD), a smaller number of therapy sessions and a mean younger age were predictors of poorer outcome.[20] Homework adherence has been shown to predict tic severity reduction [18]. In a study on predictors and moderators of behavioural intervention for anxiety disorders, higher caregiver strain predicted lower improvement.[41]

METHODS AND ANALYSIS

Design: a multi-centre, single-blinded randomised controlled trial comparing the efficacy of the Tackle
your Tics intervention (TyT, N=52) with a waiting list control group (WLCG, N=52) in children and adolescents with tic disorders.

**Participants**

Inclusion criteria: children and adolescents must meet all of the following criteria: (a) aged 9 to 17 years; (b) diagnosed with Tourette Syndrome or persistent (motor/vocal) tic disorder, using diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition[42]; (c) with at least moderate severity as indicated by a YGTSS total tic score >13 (>9 for children with motor or vocal tics only).

Exclusion criteria: (a) behavioural treatment for tics in the past 12 months; (b) pharmacological treatment for tics or another diagnosed psychiatric disorder that has not been stable the past six weeks or with planned changes during study participation; (c) poor mastery of the Dutch language; (d) IQ < 75; (e) serious physical disease; (f) substance abuse; (g) suicidality; (h) psychotic disorder; (i) poor group functioning and/or low motivation (as reported by child, parents or local therapist). Since Tourette Syndrome is seldom seen without comorbidities[15], co-occurring attention deficit–hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), anxiety disorders or mood disorders are allowed, unless the disorder requires immediate treatment or change in current treatment.

**Recruitment and randomisation**

From July 2020 to end 2022, children and adolescents are recruited by the Dutch Tourette Association and the participating expert centres on tic disorders in youth: Levvel, Accare and Yulius. After being informed by the therapist and researcher about this study, eligible participants and their parents are asked to sign informed consent forms.

Participants are randomly allocated, using block randomisation, and stratified by gender, by an independent researcher to either the brief, intensive TyT condition or the WLCG condition. The size of the blocks (2-4 patients) is randomly selected and is unknown to the researchers, to avoid allocation predictability. For each block, 50% the patients will be allocated to Tackle your Tics and 50% to the waiting list group. The randomization process is performed using a computerized data management system (Castor EDC). Patients and families are specifically instructed not to tell their condition to the researcher performing the assessments.

Patients in the TyT condition (N=52) will receive the Tackle your Tics intervention one month after randomisation, in groups of approximately 4-8 patients per group, while patients in the WLCG condition (N=52) receive this same intervention after a waiting period of 3 months (total sample: N = 104). Treatment for all participants takes place at Levvel, Amsterdam.

**Therapists and patient representatives**

The Tackle your Tics programme is provided by experienced therapists from three participating centres with expertise on tic disorders in the Netherlands: Levvel (Amsterdam), Accare (Groningen)
and Yulius (Dordrecht) together with patient representatives from the national patient organisation
(Stichting Gilles de la Tourette). Therapists are academically trained (clinical) psychologists or
cognitive behavioural therapists, with 3-15 years of experience in treating tic disorders. Co-therapists
from these sites are trained during the treatment, and have the same academical background, with less
(0-3 years of) experience in treating tic disorders. Depending on group size (4-8 participants), a team
of 2-3 experienced therapists, 1-2 co-therapists, and 1-2 trained patient representatives will provide the
treatment programme. All team members are blinded for treatment allocation of the participants.

Intervention

Behavioural therapy intervenes in the sequence of negative reinforcement between premonitory
sensations or ‘tic alarms’, the subsequent tics and decrease of the sensation. In ERP, patients with tic
disorders learn to suppress their tics for prolonged time (response prevention), while the focus remains
on these sensations (exposure). This allows the patient to learn to tolerate these sensations or ‘tic
alarms’, resulting in a reduction of tics[43][19]. The therapist coaches and encourages the patient to
improve time records, and provokes the tic alarms to optimise exposure, e.g., by attending the
sensations, playing exciting games or talking about tics.

_Tackle your Tics_ offers the same number of ERP therapy hours as regular, 12 weekly
individual ERP-sessions, but in a shorter period. The brief, intensive group programme covers three
consecutive days and one booster day one week later, followed by a ‘get together afternoon’ after one
month. The programme days consist of ERP-sessions and several supporting, relaxing, and motivating
components, to enhance motivation and homework adherence, and reduce drop out (see Table 1).

Based on our previous feasibility study, and the intensive, group-based format, we expect poor group
functioning to be the main reason for possible drop-outs.

ERP-sessions

One hour treatment sessions with ERP are offered in small subgroups of 2 or 3 children. Participants
assist each other by timing and registering their tics and encourage each other to enhance motivation
and peer support. When needed, participants can train a specific tic reduction individually with a
therapist in one of the sessions. To generalise learned skills, from about day 3 the therapist can expand
the exercises to outdoors or other situations (e.g., playing an exciting game, riding a bike), depending
on the individual progress of the participants.

Coping strategy workshops

According to a large European patient survey[26] patients need support that does not focus on tics
only but also on other symptoms and problems related to tic disorders and daily living issues (dealing
with Tourette Syndrome at home, work and school). Therefore, as advised by the Dutch national
patient association, young adult patients offer one hour coping strategy workshops each programme
day. They teach the children how to cope with their symptoms in a positive, creative way. In the workshops three themes are discussed and visualized (by writing, painting and mind mapping): self-acceptance, solution-oriented thinking and positive characteristics and strengths.

BT-Coach

A training app, BT-Coach, is introduced on the third and fourth programme day to motivate and support the children to continue with the exercises at home. The app may also be used as part of the relapse prevention plan, to enhance homework adherence after the Tackle your Tics programme has finished.[44] In the absence of a therapist, the app takes over the coaching role during homework exercises. During exposure to the premonitory urges or ‘tic alarms’ the participant records urge severity ratings. After having a tic, the participant clicks on a button ‘Tap for a Tic’ to register non-suppressed tics. The app provides visual and auditory feedback which encourages the participant to extend his or her capacity to suppress the tics and to set new time records. If the urge to tic increases, the audio-voice encourages the participant to keep suppressing the tic. If the premonitory urge to tic diminishes or is absent, it encourages exposure to the premonitory urges.”

Parent involvement

Parents are involved in the treatment by (a) parent meetings, (b) attending one therapy session to learn to coach their child during exercises and (c) participating in feedback sessions at the end of all treatment days, to evaluate and answer questions. In three parent meetings of 60 or 120 minutes (see table 1), therapists offer psychoeducation to parents, discuss expectations and how parents can help their child at home during and after treatment. Trained patient representatives accompany the meetings to exchange experiences in the parent group and offer emotional support.

Psycho-education

A small workbook, partly based on ‘Tics - workbook for children’ by Verdellen, van de Griendt and Kriens[45] has been developed specifically for this programme, to teach children and adolescents about premonitory sensations (‘tic alarms’), tic triggers, difficult moments and practicing at home. Daily psycho-education classes of 60 minutes are given jointly by therapists and patient representatives in which clinical and experiential knowledge complement each other.

Relaxation

The programme contains short (15 minutes) commonly used relaxation exercises, focusing on breathing and muscle relaxation techniques.

Covid-19 adjustments

Due to Covid-19 regulations, the first treatment groups were postponed to September 2020. The treatment programme had to be adapted according to the national pandemic regulations. We distinguish four variants of the programme: (1) the original face-to-face programme, (2) a slightly
modified programme with online parent meetings and some basic safety measures (e.g., health check), (3) a ‘blended’ programme, a mix of face-to-face and online participation, in case some participants or team members can not complete the programme face-to-face (e.g., due to quarantine), and (4) a completely online programme, if face-to-face treatment is not possible at all due to national policies (see Table 2).

**Training and treatment integrity**

Therapists of participating centres are trained in intensive ERP for tic disorders by a leading Dutch expert. Two adult experts by experience developed the coping strategy workshops and will train other patient representatives. A standardised training programme for therapists and patient representatives is used. Before the start of each treatment group, the therapists and patient representatives will be trained by experts by (1) following a three hour online training, specially developed for this study, to gain more in-depth knowledge about tics and premonitory urges, exposure and response prevention, details about the Tackle your Tics programme and research, (2) studying the protocol of the Tackle your Tics programme (time schedule, instructions for the programme elements, points of attention), and (3) attend an intervision meeting with the team of therapists and patient representatives before the start of each treatment group (to ensure treatment integrity, answer questions and share points of attention). During the treatment days, co-therapists with less experience in tic treatment will assist an experienced colleague.

To enhance treatment integrity, team intervision meetings for every new treatment group are conducted. Treatment integrity is assessed by two independent, trained raters, rating a random 20% of all programme sessions (10% TyT and WLCG condition 10%). Sessions will be audiotaped, after having received consent from patients and parents.

**Outcome measures**

At four moments, at similar time intervals for both the TyT and WLCG condition, assessments will be done pre- and post-treatment, and at 3- and 6-months follow-up, using validated, psychometrically sound instruments, with both patients, parents, and teachers as informants. See Figure 1 for the study procedure. For data management, a computerized data management system (Castor EDC) is used and monitored.

The researcher psychologist (MSc) performing the assessments will be blinded to the group conditions. Parents and patients are explicitly instructed not to communicate their group condition to the researcher. Self-report questionnaires are completed online by patients and parents. One questionnaire (Outcome Rating Scales and Session Rating scales, ORS/SRS[46]) is completed by the participants during the treatment days.
Primary outcome

Tic severity (key outcome) will be measured by the YGTSS[47], a commonly used, reliable and valid semi-structured interview for the assessment of tic severity.[48] The global tic severity score (response range 0-100) is composed of an impairment score (0-50) and a total tic score (0-50). The total tic score, the summation of the motor tic score (0-25) and the total vocal tic score (0-25), is the primary outcome measure. A high score indicates a high severity of the tics regarding number, frequency, intensity, complexity and/or interference. At T2, directly post intervention as our primary end point, we define a 25% reduction of this score as a positive response.[49]

Secondary outcomes

Quality of life is measured by the Gilles de la Tourette Syndrome Quality of Life Scale for children and adolescents; C&A-GTS-QOL[50], a 27-item patient-reported scale for the measurement of health related quality of life in patients with Tourette Syndrome (range 27-135), with high internal consistency and test-retest reliability. A high score indicates more problems in daily life and a lower quality of life.

Other secondary outcome measures are: tic-related cognitions, emotional and behavioural functioning, social competence, school functioning, self esteem, family functioning, treatment satisfaction, quality of life related to cost effectivity, and cost-effectiveness/medical consumption. For the instruments used and their psychometric characteristics, see Table 3.

Moderators and predictors

To identify possible baseline psychosocial moderators and predictors for the effectiveness of Tackle your Tics the following variables are studied for moderation and prediction: tic severity, premonitory urge severity, age, gender, family functioning, homework adherence and comorbidity (for the instruments used, see Table 3).

Patient characteristics

Demographic data are derived by the researcher from the medical files and a semi-structured interview about possible comorbid problems (Anxiety Disorder Interview Schedule; ADIS, both parent and child version (>12 years).[51] Demographical data encompass e.g., sex, gender, age in years/months, school class of child, cultural background, parental age and their marital, educational, and socio-economic status, according to the International Standard Classification of Occupations (ISCO-08)[52], psychiatric comorbidities, previous treatment of tics (behavioural therapy or medication) and outcomes thereof, family history of tics and autoimmune diseases in 1st and 2nd family relatives.

Sample size calculation

To determine the effects on the primary outcome (total tic score as measured by the YGTSS), at the primary endpoint (T2), at an effect size of Cohen’s d=0.5 (according to Cohen, 1988), with a power of
0.8, a sample size of 52 patients per group (N=104) is needed to detect univariate differences (p<0.05) between the TYT and WLCG group. In addition, we will test the background characteristics of participants versus patients who refused to participate, to determine whether there is selection bias. Based on this sample size calculation, the intervention group will encompass approximately 7-8 groups of approximately 4-8 patients with tics disorders.

Based on our clinical experiences and the percentage of dropouts in the feasibility study (7%), we aim to include and randomise at least 112 patients, to achieve the total sample size of 104, necessary to answer our research questions.

**Statistical analysis**

To check for selection bias, differences in patient characteristics between participants and non-participants (no informed consent) will be tested by independent t-tests, Chi-square tests, and Fisher’s exact tests, where appropriate. In the same way, differences in baseline characteristics will be tested between the TyT and WLCG condition.

To test the effectiveness of *Tackle your Tics*, group differences between the TyT brief intensive therapy versus WLCG at our primary outcome (T2) will be analysed using the intention-to-treat principle, by weighted generalized estimating equations (WGEEs) to handle missing data.[53] In case of treatment dropouts, the clinical measures obtained at the time of dropout will be used for our analyses. Changes on the key outcome tic severity will be corrected for group effect and analysed with Generalised Estimating Equations (GEE).

Based on the pilot study results, changes in tic severity are expected between pre (T1) and post (T2) treatment, as well as further improvement at 12 weeks (T3) and 6 months (T4) follow up. Group mean differences at the four measurements (T1-T2-T3-T4) will be tested as a secondary analysis using GEE, to show outcomes on tic severity, quality of life, premonitory urges, beliefs about tics, daily functioning: emotional/behavioural, social, and school functioning, self-esteem, family functioning (including caregiver strain), treatment alliance/satisfaction, and cost-effectivity.

To check for possible effects of the programme adjustments to Covid-19 measures (see Table 2), the differences in outcomes between the (original or slightly adapted) face-to-face groups and the blended/online groups will be analysed with GEE, as well as the differences between the results of the total study population and the study population without the participants of blended or online groups, to see if there are differences in the effects.

**ETHICS AND DISSEMINATION**

**Ethics approval**

This study is performed in accordance with the Declaration of Helsinki and approved by the medical ethical committee of the Amsterdam Medical Centre (METC nr NL66340.018.18). Representatives of
the Dutch patient organisation are active members of the research team and continuously review the research process from the patients’ perspective.

Informed consent
Oral and written information is given to parents and patients, and written consent from patients over 12 years and parents is received.

Patient and public involvement
Patient representatives are ‘experts by experience’ and play a unique and important role in this project and are equal partners in the research team from start to finish. Next to the programme contributions already mentioned, their contributions include co-designing the study, obtaining grants, recruitment, collection and interpretation of the data, co-writing publications, and giving congress presentations. This active involvement from the patient’s perspective ensures that the research process matches the needs and wishes of patients and families.

Dissemination
Results of the study will be presented on national and international conferences, peer reviewed scientific journals, patient organisation meetings and public media. If Tackle your Tics proves to be effective, the programme will be implemented in centres for youth mental health care.

DISCUSSION
This study is, to our knowledge, the first randomised controlled trial studying the effectiveness of a brief, intensive group-based exposure therapy for children and adolescents with chronic tic disorders. If this brief, intensive ERP treatment is shown to be effective, it can offer several benefits. Programmes like Tackle your Tics can expand the access to behavioural treatment for youth living in different areas, where specialised therapists trained in treatment of tics are unavailable. Families may find it more feasible to follow a brief, compromised treatment in four days with earlier benefit of possible treatment results and additional support. The programme also offers opportunities to educate behavioural therapists in behavioural (group) therapy for tics. This study will show which children benefit most from an intensive group-based format, which will make it easier for practitioners to give personalised treatment advice.

This study design also encompasses several limitations. First, the active treatment condition is compared with a waiting list condition, in which the participants receive the same treatment after three months. No active control condition is being compared. As a consequence, no conclusions can be drawn about the value of the specific components of the programme.
Second, the results of this trial may not be directly generalisable to all patients in clinical practice, since the parents and children in this sample were motivated to participate in research, preferred an intensive group-based treatment and were able to invest time and effort to travel to the treatment centre. Furthermore, it is unclear what the effectiveness will be on the longer term, since the last follow-up measurement is conducted six months after treatment. Lastly, effects of programme adjustments and family stress as a result of the Covid-19 pandemic may influence treatment results but will also provide new insights into the feasibility to adjust group programmes during changing situations.

Few studies have investigated the neural changes that are associated with behavioural treatment for tics. A study of Deckersbach et al. (2014) indicated that behavioural therapy leads to a normalization of activation in the putamen.[54] Future studies could provide more insight into the mechanisms of behavioural therapy and its components.

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Authors’ contributions
APH, CH, CWJV, JMTMG, LPLB, KJK, RJLL, DC, PJH, and EMWJU contributed to the design of the study. APH drafted the article. All authors revised the article critically and approved the final version.

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Conflicts of interest
CWJV and JMTMG developed and published the manual ‘Tics’ and the training app BT-Coach (BT-Tics Foundation), which are both being used in the programme. On behalf of all authors, the corresponding author states that there are no other conflicts of interest.
### Tables and figures

#### Table 1: *Tackle your Tics* therapy programme for children and adolescents

Three parallel parent meetings are organised on day 1 and day 4 (10:00-12:00) and on the ‘get together afternoon’ (15:45-16:45). Psychoeducation and workshops are offered in subgroups of 3-5 children, parallel to the ERP sessions of the other participants (except for small groups that consist of 4 or 5 children).

| Time          | Day 1                                                                 | Day 2                                                                 | Day 3                                                                 | Day 4 booster day (after 1 week) | Get together afternoon (after 1 month) |
|---------------|----------------------------------------------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------|-----------------------------------|---------------------------------------|
| 9:30-10:00    | Welcome and acquaintance game (all participants and parents)          |                                                                      |                                                                      |                                   |                                       |
| 10:00-11:00   | Psychoeducation or therapy session (subgroups)                        | Psychoeducation or therapy session (subgroups)                       | Psychoeducation or therapy session (subgroups)                       | Psychoeducation or therapy session (subgroups) |
| 11:00-11:10   | Short break (all participants)                                        | Short break (all participants)                                       | Short break (all participants)                                       | Short break (all participants)    |
| 11:10-12:10   | Psychoeducation or therapy session (subgroups)                        | Psychoeducation or therapy session (subgroups)                       | Psychoeducation or therapy session (subgroups)                       | Psychoeducation or therapy session (subgroups) |
| 12:10-12:40   | Lunch break (all participants)                                        | Lunch break (all participants)                                       | Lunch break (all participants)                                       | Lunch break (all participants)    |
| 12:40-13:40   | Workshop coping strategies or therapy session (subgroups)             | Workshop coping strategies or therapy session (subgroups)            | Workshop coping strategies or therapy session (subgroups)            | Workshop coping strategies or therapy session (subgroups) |
| 13:40-14:10   | Playtime (all participants)                                           | Playtime (all participants)                                           | Playtime (all participants)                                           | Playtime (all participants)      |
| 14:10-15:10   | Workshop coping strategies or therapy session (subgroups)             | Workshop coping strategies or therapy session (subgroups)            | Workshop coping strategies or therapy session (subgroups)            | Workshop coping strategies or therapy session (subgroups) |
| 15:10-15:25   | Relaxation therapy (all participants)                                 | Relaxation therapy (all participants)                                 | Relaxation therapy (all participants)                                 | Relaxation therapy (all participants) |
| 15:25-15:40   | group therapy session (all participants)                              | group therapy session (all participants)                              | group therapy session (all participants)                              | group therapy session (all participants) |
| 15:40-15:55   | Short evaluation (all participants)                                   | Short evaluation (all participants)                                   | Short evaluation (all participants)                                   | Short evaluation (all participants) |
| 15:55-16:30   | Feedback: therapist with parents and participant                      | Feedback: therapist with parents and participant                      | Feedback: therapist with parents and participant                      | Feedback: therapist with parents and participant |
|               |                                                                      |                                                                      |                                                                      | Get together (participants and parents): welcome                                |
|               |                                                                      |                                                                      |                                                                      | 14:00-14:30                       |
|               |                                                                      |                                                                      |                                                                      | Evaluation (participants and parents)                                            |
|               |                                                                      |                                                                      |                                                                      | 14:30-15:30                       |
|               |                                                                      |                                                                      |                                                                      | Break/playtime                     |
|               |                                                                      |                                                                      |                                                                      | 15:30-15:45                       |
|               |                                                                      |                                                                      |                                                                      | Workshop (all participants)                                                  |
|               |                                                                      |                                                                      |                                                                      | 15:45-16:45                       |
|               |                                                                      |                                                                      |                                                                      | Get together (participants and parents): closing                                |
|               |                                                                      |                                                                      |                                                                      | 16:45-17:00                       |
Table 2: Adjustments to Covid-19 measures on the *Tackle your Tics* programme

| Indications                                      | Original programme (see table 1) | Adapted programme | Blended programme                                                                 | Online programme                                                                 |
|-------------------------------------------------|----------------------------------|-------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| If no Covid-19 regulations are applicable        |                                  |                   | If some participants or team members cannot continue participation after a face-to-face start, e.g.: due to quarantine or positive test | If face-to-face group treatment is impossible from the start due to policy changes |
| In case of applicable Covid-19 regulations      |                                  |                   |                                                                                  |                                                                                  |

| Programme elements for participants             | Face-to-face                      | Face-to-face, with adjustments based on national Covid-19 regulations, e.g.: health check, protective equipment, larger spaces, ventilation | Mix of face-to-face with Covid-19 adjustments and online participation | Completely online, in shortened form |
|-------------------------------------------------|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| Face-to-face parent meetings in parallel during the children’s programme, face-to-face parent sessions and feedback sessions with the therapist |                                  |                                                                                                                                  |                                                                                    |                                    |

| Programme elements for parents                  | Online parent meetings in the evenings, face-to-face parent sessions and feedback sessions with the therapist | Online parent meetings in the evenings, face-to-face or online parent sessions and feedback sessions with the therapist | Online parent meetings in the evenings, online parent sessions and feedback sessions with the therapist |
|-------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| Online parent meetings in the evenings, face-to-face or online parent sessions and feedback sessions with the therapist |                                                                    |                                                                                                                                  |                                                                                    |                                    |
Table 3: Assessment plan for the *Tackle your Tics* study (N=104) at four assessment moments (N=104)

| Variable                        | Questionnaire                                                                 | Items | Score range | Score indication                             | Assessment moments |
|---------------------------------|-------------------------------------------------------------------------------|-------|-------------|---------------------------------------------|--------------------|
| **Primary outcome**             |                                                                                |       |             |                                             |                    |
| Tic severity*                   | Yale Global Tic Severity Scale (YGTSS)[47]                                   | 11    | 0-100       | Low-high tic severity                        | R R R R            |
| **Secondary outcomes**          |                                                                                |       |             |                                             |                    |
| Quality of life                 | Gilles de la Tourette Syndrome Quality of Life Scale for children and adolescents (C&A-GTS-QOL)[50] | 27    | 27-135, scale scores | Low-high degree of problems in daily life (= high-low quality of life) | C C C C            |
| Tic-related cognitions         | Beliefs about Tics Scale (BATS)[55] (Dutch translation)                      | 20    | 20-80       | Low-high degree of tic-related cognitions   | C C C C            |
| Emotional/behavioural functioning | Child Behavior Checklist (CBCL-18)[56,57]                                    | 112   | 0-220       | Low-high degree of emotional and behavioural problems | P P P P            |
| Emotional/behavioural functioning | Youth-Self Report (11y and older) (YSR) [57]                                | 112   | 0-220       | Low-high degree of emotional and behavioural problems | C C C C            |
| School functioning             | Teacher Report form [TRF][57]                                                | 112   | 0-220       | Low-high degree of emotional and behavioural problems | T T T T            |
| Self esteem                     | Self Perception Profile for Children[58] (Dutch versions for children or adolescents: CBSK, CBSA)[59] | 36   | scale scores | Low-high experience of competence and self esteem | C C C C            |
| Quality of life related to health | EQ-5D /EQ-5D-Y[60–62]                                                         | 5     | 1-5 per item | Low-high health related quality of life      | C,P C,P C,P C,P    |
| Stress of parenting            | Stress of parenting questionnaire (OBVL)[63]                                 | 34    | 34-136      | Low-high stress of parenting                 | P P P P            |
| Care-related quality of life in informal caregivers (parents) | Care Related Quality of Life (CarerQoL)[64]                                | 7     | 0-100       | Low-high burden of providing informal care   | P P P P            |
| Cost-effectiveness/medical consumption | Treatment Inventory of Costs in Patients with psychiatric disorders (TIC-P) /TIC-P-Y[65] | 57    |             | Low-high medical costs and productivity losses | C,P C,P C,P C,P    |
| Treatment satisfaction/burden/homework adherence | Treatment satisfaction forms, developed for this study (child/parent version) | 17 (C) | 11-55       | Low high treatment satisfaction              | C,P C,P C,P C,P    |
| Moderator/predictor variables | Therapeutic alliance, patient functioning | Outcome Rating Scales and Session Rating scales[46] (during treatment, child/youth version) | 8 | 0-40 per scale | Low-high |
|-------------------------------|------------------------------------------|-----------------------------------------------------------------------------------|---|----------------|---------|
| Moderator/predictor variables | Demographic data | Sex, gender, age | | R, | P |
| Moderator/predictor variables | Family functioning | Family Assessment Device[66] (general functioning subscale) | 12 | 12-48 | Low-high degree of problems in family (high-low family functioning) | P | P | P |
| Moderator/predictor variables | Psychiatric comorbidities | Anxiety Disorders Interview Schedule[51] | 0-8 severity score per comorbidity | Comorbidities and low-high severity | C, | P |
| Moderator/predictor variables | Premonitory urges | Premonitory Urges for Tics Scale[67] | 9 | 9-36 | Low-high tic-related feelings and sensations (premonitory urges) | C* |

Abbreviations: P=parent report, C=child report, T=teacher report, R=researcher/clinician report
*Tic severity at baseline and homework adherence will also be included in the moderator/predictor analyses (see Methods and Analysis)

Supplementary Figure legend

Figure 1: Flowchart study procedure *Tackle your Tics*
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Figure 1: study procedure

282x539mm (300 x 300 DPI)
SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Page/line |
|--------------|---------|-------------|-----------|
| Administrative information |          |             |           |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2/61 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | NA |
| Protocol version | 3 | Date and version identifier | 2/55 |
| Funding | 4 | Sources and types of financial, material, and other support | 14/434 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1/10 |
| | 5b | Name and contact information for the trial sponsor | 14/434 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 14/434 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 14/434 |
| Introduction |          |             |           |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 3/68 |
| | 6b | Explanation for choice of comparators | 5/116 |
| Objectives | 7 | Specific objectives or hypotheses | 5/134 |
Trial design  8  Description of trial design including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, non-inferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting  9  Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

Eligibility criteria  10  Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)

Interventions  11a  Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

  11b  Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)

  11c  Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)

  11d  Relevant concomitant care and interventions that are permitted or prohibited during the trial

Outcomes  12  Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

Participant timeline  13  Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)

Sample size  14  Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations

Recruitment  15  Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:
### Sequence generation 16a
Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions.

### Allocation concealment mechanism 16b
Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned.

### Implementation 16c
Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions.

### Blinding (masking) 17a
Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how.

### Blinding (masking) 17b
If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial.

### Methods: Data collection, management, and analysis

#### Data collection methods 18a
Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol.

#### Data collection methods 18b
Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols.

#### Data management 19
Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol.

#### Statistical methods 20a
Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol.

#### Statistical methods 20b
Methods for any additional analyses (eg, subgroup and adjusted analyses).

#### Statistical methods 20c
Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation).
Methods: Monitoring

Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed 10/295

21b Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial 12/380

Harms 22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct 12/380

Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor 12/380

Ethics and dissemination

Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval 12/377

Protocol amendments 25 Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) 12/377

Consent or assent 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) 12/384

26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable NA

Confidentiality 27 How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial 12/377

Declaration of interests 28 Financial and other competing interests for principal investigators for the overall trial and each study site 14/440

Access to data 29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators 12/377

Ancillary and post-trial care 30 Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation 12/377
### Dissemination policy

- **31a**: Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions

- **31b**: Authorship eligibility guidelines and any intended use of professional writers

- **31c**: Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

### Appendices

| Category            | Item | Description                                                                                     | Page |
|---------------------|------|-------------------------------------------------------------------------------------------------|------|
| Informed consent    | 32   | Model consent form and other related documentation given to participants and authorised surrogates | App  |
| Biological specimens| 33   | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | NA   |

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