Therapist-supported online remote behavioural intervention for tics (ORBIT) in children and adolescents: A single-blind randomised controlled trial

Authorship line:

Chris Hollis (*FRCPsych*) [1,2,3,9], Charlotte L Hall (*PhD*) [1,3], Rebecca Jones (*MSc*)[4], Louise Marston (*PhD*) [5], Marie Le Novere (*MSc*) [5], Rachael Hunter (MSc) [5], Beverley J Brown (*PhD*) [1], Charlotte Sanderson (*DClinPsy*) [6,7], Per Andrén (*MSc*) [8], Sophie D Bennett (*PhD*) [6,7], Liam R Chamberlain (*BSc*)[1], E Bethan Davies (*PhD*) [1,3], Amber Evans (*MSc*) [6,7], Natalia Kouzoupi (*MSc*) [6,7], Caitlin McKenzie (*MSc*)[1], Isobel Heyman (*PhD*)[6,7], Kareem Khan (*MSc*)[1], Joseph Kilgariff (*BA*)[9], Cristine Glazebrook (*PhD*) [1,3], David Mataix-Cols (*PhD*) [8], Tara Murphy (*DClinPsy*) [6,7], Eva Serlachius (*PhD*) [8], Elizabeth Murray (*PhD*) [5]

Affiliations:

[1] NIHR MindTech MedTech Co-operative, Institute of Mental Health, School of Medicine, University of Nottingham, Innovation Park, Triumph Road, Nottingham, UK

[2]NIHR Nottingham Biomedical Research Centre, Institute of Mental Health, University of Nottingham, Innovation Park, Triumph Road, Nottingham, UK

[3]Mental Health and Clinical Neurosciences, School of Medicine, University of Nottingham, Queen's Medical Centre, Nottingham, UK

[4]Division of Psychiatry and Priment CTU, University College London, 6th Floor Maple House, 149 Tottenham Court Road, London, UK

[5]Research Department of Primary Care and Population Health and Priment CTU, University College London, Upper 3rd Floor, Royal Free Campus, Rowland Hill Street London, UK

[6]UCL Great Ormond Street Institute of Child Health (ICH), 30 Guilford Street, London WC1N 1EH, UK/Great Ormond Street Hospital for Children NHS Trust, Great Ormond Street, London, UK.

[7]Psychological and Mental Health Services, Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond Street, London, UK

[8]Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, and Stockholm Health Care Services, Region Stockholm, Stockholm, Sweden

[9]Department of Child and Adolescent Psychiatry, Nottinghamshire Healthcare NHS Foundation Trust, South Block Level E, Queen's Medical Centre, Nottingham

Corresponding author:

Professor Chris Hollis

Chris.hollis@nottingham.ac.uk

Institute of Mental Health, Mental Health and Clinical Neurosciences, University of Nottingham, Innovation Park, Triumph Road, Nottingham, NG7 2TU, UK

SUMMARY

Background: Exposure and Response Prevention (ERP) for tics appears a promising form of behaviour therapy for online delivery which could widen access to treatment. However, the effectiveness of ERP in general, and in particular when delivered online, remains uncertain. We evaluated the effectiveness of internet-delivered, therapist-supported and parent-assisted ERP for tics.

Methods: Multi-centre, parallel group, single-blind, randomised controlled trial. Eligible participants were aged 9-17 years with Tourette syndrome/chronic tic disorder, who had not received behaviour therapy for tics within 12 months, and had a Yale Global Tic Severity Scale (YGTSS) Total Tic Severity Score (TTSS) of >15, or >10 if motor or vocal tics only. Participants were recruited via 16 patient identification centres, two study sites in England (Nottingham and London), or online self-referral, and were randomised (1:1) by blinded outcome-assessors to receive either 10 weeks of ERP or psychoeducation (active control). The primary outcome was YGTSS-TTSS at 3 months' post-randomisation, analysis was by intention-to-treat. The mean cost per patient for the intervention were calculated. Longer term follow-ups are still on-going. Registrations are ISRCTN (ISRCTN70758207) and ClinicalTrials.gov (NCT03483493).

Findings: Between 8th May 2018 and 30th September 2019, 224 participants were enrolled; 112 to ERP and 112 to psychoeducation. The sample was predominately male (177; 79%) and of white ethnicity (195; 87%). The difference between the groups on the YGTSS-TTSS was -2.29 points (95% CI: -3·86 to -0·71), a reduction favouring the ERP intervention at 3 months, an effect that increased by 6 months post-randomisation (-2·64, 95% CI: -4·56 to -

0·73). The average therapist time spent supporting the intervention was 2·5 hours. The additional cost per participant of the ERP intervention compared to psychoeducation was £159 (95% CI -£53 to £370). There were two unrelated serious adverse events, both in the psychoeducation group.

Interpretation: ERP is an effective behavioural therapy for tics. Digitally enabled ERP with minimal therapist contact time represents an efficient public mental health approach to improve access to behavioural therapy for tics in children and adolescents.

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INTRODUCTION

Tic disorders such as Tourette syndrome (TS) or chronic tic disorder (CTD) are common conditions affecting up to 1% of young people.[1] Tics can lead to significant impairment and isolation[2] and often co-occur with other conditions. Although there are effective pharmacological treatments for tics, they are associated with side-effects such as weight-gain and cognitive dulling.[2] Behavioural therapies for tics include: Habit Reversal Training (HRT), where patients learn to detect tics and use a competing response (an incompatible action) to control them; Comprehensive Behavioural Intervention for Tics (CBIT) which combines HRT with relaxation, functional analysis and social support; and Exposure and Response Prevention (ERP), where patients learn to suppress their tics (response prevention) while tolerating urges to tic (exposure). Unlike HRT/CBIT, no competing response is trained in ERP, potentially making it easier to deliver with minimal therapist input.

Evidence of the effectiveness of behavioural therapy (BT) for tics is drawn primarily from two large superiority trials of CBIT in children/adolescents[3] and adults[4] conducted in the United States. In contrast, ERP has been less well evaluated and its superiority for tics against

an active control intervention is unknown. One small pilot (N = 23) head-to-head comparison between ERP and HRT showed a similar reduction in tic symptoms but was underpowered to demonstrate non-inferiority between the treatments.[5]

Although behaviour therapy (HRT/CBIT) for tics has demonstrated similar effectiveness to pharmacotherapy[2] and is recommended as a first line intervention [1,2] it is rarely available. In the United Kingdom (UK), only one in five children and adolescents with tic disorders has access, with less than half of them receiving the recommended number of sessions.[6] Barriers include a shortage of trained therapists, and therapy only being offered at specialist treatment centres meaning patients often have to travel long distances. The COVID-19 pandemic has further highlighted the urgent need to offer cost-effective interventions that can be delivered remotely in digital formats.[7]

Across different mental health conditions, meta-analyses demonstrate that online internet-delivered cognitive behavioural therapy (iCBT) is as efficacious as face-to-face delivery and can result in substantial cost-savings.[8] Evidence from studies of internet-delivered, cognitive behavioural therapy (iCBT) with adults suggests that therapist-guided interventions lead to better outcomes[9] than standalone iCBT. Given the lack of specialist child therapists in this area, a blended approach of digitally enabled therapy whereby the core therapeutic content is delivered online in a standardised chapter format, but is supported asynchronously by a non-specialist therapist, whose primary role is to promote engagement may offer a more pragmatic solution. A meta-analysis of CBT for anxiety and depression in children argued that parents are also a potentially valuable but under researched resource to support the delivery of iCBT in children.[10]

Recent research in Sweden has developed an online platform to deliver therapist-supported iCBT called “BIP” (*Barninternetprojektet* [Child Internet Project]; http://www.bup.se/bip).

The platform has been used to deliver therapy to children with a range of mental health conditions, including anxiety, and obsessive-compulsive disorder.[11,12] Compared to other conditions, internet delivery of therapy for tics has received less interest.[13] One small pilot study using the BIP platform compared 10 weeks of therapist-guided, parent-supported HRT against ERP in children and adolescents with tics who were followed-up at 3 and 12 months post-treatment. The findings indicted that the method of delivery was highly acceptable to families. Whilst both therapeutic groups demonstrated a reduction in tic severity and impairment and improved quality of life, only the group who received ERP experienced a significant reduction in tic severity.[14] Although this pilot study was not designed or powered to evaluate efficacy, the results support the feasibility and promise of online ERP for treating tics and justify further investigation to assess clinical effectiveness and cost-effectiveness. In the present study, we aimed to evaluate the clinical effectiveness and costs of a therapist-supported, parent-assisted internet-delivered ERP programme for tics in children and adolescents in the UK.

METHODS

Study design and participants

The Online Remote Behavioural Intervention for Tics (ORBIT) trial was a two-arm, superiority parallel group, single-blind, multi-centre randomised control trial (RCT). It commenced on 1st October 2018 with an anticipated completion date of 30th September 2021. The trial was conducted across two Child and Adolescent Mental Health Services (CAMHS) in England. Site one (Queen's Medical Centre, Nottingham) was based in a mid-sized city and was a regional centre for tic treatment. Site two (Great Ormond Street Hospital, London) was a large metropolitan national paediatric centre of excellence.

The trial had two phases: Phase 1, a per-protocol follow-up for 6 months post-randomisation and Phase 2, a naturalistic follow-up for 18 months post-randomisation. The findings from Phase 1 are presented here.

Ethical and Health Research Authority (HRA) approval was received from North West Greater Manchester Research Ethics Committee on 23 March 2018 (ref.:18/NW/0079). The published trial protocol is available online[15] and was approved by an independent trial steering committee (TSC) and data monitoring committee (DMC). Two substantial amendments were made and can be found in the appendix p1. The trial was prospectively registered with the ISRCTN (ISRCTN70758207) and ClinicalTrials.gov (NCT03483493).

Eligible participants were aged 9-17 years with a moderate/severe tic disorder (TS or CTD) defined as scores on the Yale Global Tic Severity Scale (YGTSS)[16] Total Tic Severity Score (TTSS) of >15, or >10 if only motor or vocal tics were present in the last 7 days. All participants were required to have broadband and smart phone/regular desktop/laptop computer access and the capacity to provide informed, written consent. Participants aged under 16 years were required to have a parent/guardian consent and provide their own assent. Participants aged 16-17 years signed their own consent and have parent/guardian consent.

Exclusion criterion were: engaged in structured behavioural intervention for tics (e.g., HRT/CBIT or ERP) within the preceding 12 months or about to start; changed (i.e. starting or stopping) medication for tics within the previous two months; alcohol/substance dependence, psychosis; suicidality or anorexia nervosa (assessed via the Development and Well Being Assessment - DAWBA),[17] suspected moderate/severe intellectual disability (assessed via Child and Adolescent Intellectual Disability Screening (CAIDS-Q)[18], immediate risk to self or others; parent/carer of child unable to speak or read/write English.

Participants were recruited either by referral from one of 16 participating CAMHS or community paediatric clinics in England and the two study sites or by self-referral via Tourettes Action (UK tic disorder charity) website or the study website. Researchers (outcome assessors) completed an initial telephone consultation to determine likely eligibility and parents/carers completed the online DAWBA. Potential participants deemed eligible after this initial screen attended a baseline assessment at one of the two study sites where assessors conducted further eligibility assessments including the YGTSS and CAIDS-Q. Written informed consent was obtained from participants and/or their parents/carers prior to undertaking the baseline assessment.

Randomisation and masking

Participants were randomly allocated in a 1:1 ratio to receive either 10 weeks of online, remotely delivered, therapist-supported ERP for tics or therapist-supported education about tics, referred to as psychoeducation (the active control). Outcome assessors randomly assigned participants using a secure web-based randomisation system developed by Sealed Envelope (https://www.sealedenvelope.com/) and managed by Priment Clinical Trials Unit, following specified standard operating procedures. Randomisations were stratified by study site using block randomisation with varying block sizes. Therapists and an independent assessor who did not conduct outcome assessments were informed of the allocation via email. The independent assessor verified that each participant was assigned to their allocated intervention – no instances of incorrect allocation were observed. Outcome assessors, statisticians, health economists, the trial manager and chief investigator were blind to group allocation. Participants were not directly informed of their allocation by either the researcher or the therapist, however, they may have been able to determine allocation from the content once treatment commenced. Participants were reminded about the importance of masking at

each follow-up, however, four instances of breaks of allocation concealment were reported to the trial manager. In all instances the child disclosed information about their treatment to the outcome assessor at the end of the follow-up assessment. In these cases, subsequent follow-ups were conducted by an alternative, blinded assessor. All instances were reviewed by the independent TSC and DMC for monitoring.

Procedures

The treatments were delivered via the secure online Swedish "BIP" platform. Participants and their parent/carers created their log-in details at the baseline assessment and set a treatment start date within 1-week of randomisation. Where possible, participants were briefly introduced to their therapist in person at the baseline assessment. At the baseline assessments for each site, researchers went through the eligibility criteria and obtained informed consent. Further preliminary measures were conducted including demographics, Child and Adolescent Service Use Schedule (CA-SUS),[19] Children's Global Assessment Scale (CGAS),[20] exposure to concomitant interventions and the CAIDS-Q. The CAIDS-Q was to further establish eligibility for treatment. The researchers then conducted the YGTSS assessment to determine presence and severity of tics as per the protocol inclusion criteria. All researchers undertook extensive YGTSS training and supervision sessions. Training and supervision was delivered by an expert clinician in the delivery and evaluation of the primary measures. All researchers had to reach a specified level of expertise prior to the initiation of baseline assessments. The therapists assigned the participant to their allocated treatment and emailed a reminder to log in on their start date. The treatment content has been described elsewhere.[15] In summary, information was presented in chapters, which the family (child/adolescent and parent/carer) were requested to work-through. The therapist aimed to have 10-20 minutes contact time with the participants (combined contact time with the parent/carer and/or child/adolescent) each

week to check progress, encourage motivation and answer questions, but did not deliver therapeutic content. Both the ERP intervention and the psychoeducation consisted of 10 chapters for the child/adolescent and 10 different chapters for parent/carers, designed to be delivered over 10 weeks. The therapist provided support for either ERP or psychoeducation through asynchronous contact (typically delivered via online messages sent through BIP) during these 10 weeks.

The internet-delivered ERP intervention was adapted from previously published treatment manuals by Verdellen et al.[21] Participants were requested to first practice controlling all of their tics for increasingly long periods of time (response prevention), and then to deliberately provoke the premonitory urges whilst not releasing any tics (exposure and response prevention). All tics were targeted at the same time. Specific triggers to provoke the urge to tic were identified and used by participants, and then employed in everyday situations to improve generalisability of the gains. The psychoeducation comparator focussed on the history, prevalence and risk typically associated with tic disorders, and advised healthy habits, with no information on tic control. For both interventions, the main treatment information was delivered via ten child-completed chapters; participants were considered "treatment completers" if child chapters 1-4 were completed. The first 4 chapters included the active exposure and response prevention components of the intervention and were thus considered the minimum therapeutic dose. The 10 parent chapters focused on how best to support the child during their treatment.

Therapists (graduate level education) were not required to have previous experience in treating tic disorders but were trained on the platform and its contents and received regular expert supervision. Further details can be found elsewhere.[22] As the therapists did not deliver active therapeutic content it was not necessary to account for potential therapist effects in statistical analysis. Participants completed brief online measures mid-point through treatment

(3 and 5 weeks) and completed online and outcome-assessor rated measures at baseline, 3, 6, 12 and 18 months' post-randomisation. All follow-up outcome-assessor rated measures were completed remotely (via videoconferencing or telephone). Only the baseline appointment was conducted in person at one of the two study sites.

Outcomes

The primary outcome was tic severity at 3 months post-randomisation as measured by the YGTSS-TTSS. This is a semi-structured interview that combines separate scales of motor tics (score 0-25) and vocal tics (score 0-25), providing a total score 0-50, with higher scores indicating greater severity. The YGTSS-TTSS is the gold standard measure of tics used widely in clinical practice and research. It is freely available in the public domain and has been translated into many languages. A systematic review[1] found the average estimate for the standard deviation (SD) of the YGTSS-TTSS from 19 trials of behavioural intervention for tics was 6·6 (mean TTSS score was 23 to 25). The YGTSS-TTSS was completed by a blinded outcome-assessor. All outcome-assessors completed mandatory structured training on the YGTSS prior to starting and agreement with an expert rater was assessed every 6 months; full details can be found in appendix p2.

Secondary outcomes were obtained at baseline, 3 and 6 months' post-randomisation, through interviews conducted by the blinded outcome assessors with the parent/carer and child/young person. They comprised: reduction in tic related impairment assessed through the YGTSS impairment scale (score 0-50); a global assessment of symptom improvement measured via the Clinical Global Impressions - Improvement scale (CGI-I),[23] and global functioning assessed via the CGAS; service use using a modified version of the CA-SUS to include specific specialist tic disorder services and medications.

Parent/carers completed secondary outcomes online including measures of general behavioural and emotional difficulties (Strengths and Difficulties Questionnaire; SDQ),[24] generic health-related quality of life (proxy-rated child-health-utility-9D; CHU9D),[25] adverse events or side-effects (modified version of the Hill and Taylor[26] side-effects scale). A parent assessment of tics measured via the Parent Tic Questionnaire (PTQ)[27] was completed at these times and also at 5 weeks (mid-treatment).

Additional outcomes completed online by the child/adolescent included: generic quality of life (CHU9D) and a disease-specific measure of quality of life (Child and Adolescent Gilles de la Tourette Syndrome Quality of Life Scale; C&A-GTS-QOL).[28] Two additional measures were completed by the child/adolescent at 5 weeks (mid-treatment) as well as at baseline, 3 and 6 months, namely the Mood and Feelings Questionnaire (MFQ)[29] and the Spence Childhood Anxiety Scale (SCAS)[30]. For the purpose of this study, a measure of treatment credibility was developed and completed online by parent/carers and child/adolescent at 3 weeks.[15] Premonitory urges were recorded at baseline using the Premonitory Urge for Tics Scale (PUTS)[31].

Adverse events and side-effects were formally sought and recorded at each follow-up through the side-effects scale and MFQ. Participants were also encouraged to report them to their therapist or outcome assessor (see appendix p5-6).

Statistical analysis

Based on findings of other trials, the sample size was calculated in order detect a clinically important average difference of 0·5 of a standard deviation between ERP and psychoeducation with 90% power at $p<0·05$ (two-sided). When allowing for 20% dropout, this required a total sample size of 220 participants.

Statistical analyses were conducted using Stata (version 16) in line with a predefined statistical analysis plan (SAP) approved by the TSC. Analysis was performed on an intention-to-treat basis, in which participants were analysed according to their allocated group. In line with the SAP, confidence intervals are reported rather than p-values.

Baseline demographic characteristics of participants, as well as their clinical and mental health outcomes at baseline and 3 and 6 months follow up, were summarised by randomised group using mean (standard deviation [SD]) or count (percentage) respectively for continuous and categorical data. The primary outcome was estimated using a linear regression model with YGTSS-TTSS at 3 months as the outcome and study group as the main explanatory variable, adjusting for YGTSS-TTSS at baseline and site (Nottingham/London).

Similar linear regression models were fitted to estimate the effect of the intervention on secondary outcomes at mid-treatment, 3 months and 6 months follow up (post-randomisation). The statistical model for the CGI-I did not adjust for baseline since this is a measure of change. Using CGI-I to indicate response to treatment, the scale was dichotomised to define response as ‘improved’ or ‘much improved’ versus non-response as ‘minimally improved’, ‘stayed the same’, ‘worse’ or ‘very much worse’. Two unplanned subgroup analyses explored whether the effect of the intervention on the primary outcome was modified by either anxiety diagnosis or attention deficit hyperactivity disorder (ADHD) diagnosis. The statistical models were the same as for the main analysis of the primary outcome, with the addition of a fixed effect of the comorbidity (anxiety or ADHD) and an interaction between the comorbidity and study arm. All statistical analyses were complete case.

A separate full economic evaluation will be conducted at the end of the 18-month follow-up (Phase 2) as the follow-up duration of 6-months is insufficient for calculating an incremental cost per quality-adjusted life year (QALY) gained. Here we explore the cost of delivering the

ERP and psychoeducation interventions, examine relevant healthcare resource use, and evaluate the suitability of the CHU9D for calculating QALYs in an 18-month analysis. Further details on the method and findings can be found in the appendix (p8-23).

Role of the funding source

The study was publicly funded by the UK National Institute for Health Research (NIHR) Health Technology Assessment (Ref: 16/17/02). The funders had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

RESULTS

Participant enrolment began on 8th May 2018 and ended 30th September 2019. The last participant completed the 6-month follow-up on 30th April 2020; at this point Phase 1 of the ORBIT trial was completed. Of the 445 potential participants who registered their interest in the trial, 210 were excluded following an initial telephone screen and/or DAWBA results, thus 235/445 (52·8%) attended a baseline assessment and were consented into the trial. Eleven were found ineligible after the further screening measures; thus 224/445 (50·3%) potential participants were randomised, of whom 112/224 (50·0%) were assigned to the ERP intervention and 112/224 (50·0%) were assigned to the psychoeducation group. Figure 1 shows the flow of participants through the trial.

Participants had a mean age of 12 years, were predominately male (177/224; 79%) and defined their ethnicity as white (195/224; 87%). Only 13% (30/224) of participants were receiving medication for tics (Table 1). Premonitory urges (PUTS score) measured at baseline was similar across the intervention group (mean = 22, SD = 7) and psychoeducation group (mean = 21, SD = 6), equating to medium intensity for premonitory urges. Baseline scores on the primary and secondary outcome measures were similar across the trial arms (Table 2).

Primary outcome data were collected from 99/112 (88·4%) in the intervention group and 105/112 (93·7%) in the psychoeducation group. The only predictor of missingness was site, which was included as a covariate in the statistical model.

Mean YGTSS-TTSS at 3 months in the ERP group was 23·9 (SD: 8·2) compared to 26·8 (SD: 7·3) in the psychoeducation group. The mean total decrease YGTSS-TTSS at 3-months was 4·5 (16%) for ERP vs 1·6 (6%) for psychoeducation, and at 6 months was 6·9 (24%) for ERP vs 3·4 (12%) for psychoeducation. The adjusted (for baseline and site) analysis of the primary outcome at 3 months revealed that the ERP intervention reduces YGTSS-TTSS by -2·29 points (95% CI: -3·86 to -0·71) in comparison to the psychoeducation with an effect size (ES) of -0·31 (95% CI -0·52 to -0·10) (Table 2).

This adjusted effect on tics (YGTSS-TTSS) was slightly increased at 6 months (estimated difference: -2·64; 95% CI: -4·56 to -0·73) with an ES of -0·36 (95% CI -0·62 to -0·10). Figure 2 presents a forest plot of standardised effect sizes for primary and secondary outcomes.

The secondary outcome of parent reported tic (PTQ) symptoms supported the primary outcome finding at 3 months (-9·44; 95% CI: -15·37 to -3·51) and 6 months (-8·60; 95% CI: -14·43 to -2·77). There was no statistically significant difference in tic related impairment as measured by the YGTSS impairment scale at either time point (Table 2).

Other secondary outcomes including parent-reported general emotional and behavioural functioning (SDQ), young person reported low mood (MFQ) and outcome assessor reported overall functioning (CGAS) were not significantly different between the two groups at 3 or 6 months. Although there was no difference in young person reported anxiety (SCAS) at 3 months, there was a difference in favour of the ERP group at 6 months (-5·10; 95% CI: -9·70 to -0·50). Conversely, the young person reported tic-specific quality of life (C&A-GTS-QOL) and the outcome-assessor completed perception of global improvement (CGI-I) showed superior results in the ERP group than psychoeducation at 3 months (CGI -0·41; 95% CI: -0·71 to -0·11. C&A GTS-QOL -4·81; 95% CI: -8·79 to -0·83) but no difference at 6 months.

There was no difference in scores on the MFQ or PTQ at the mid-point of the intervention (see appendix p.25). A further unplanned post-hoc analysis revealed no evidence to suggest that the ERP therapy had a different effect either in participants with or without a comorbid anxiety disorder or with or without comorbid ADHD (see appendix p.25). An additional unplanned analysis (see Table 3) comparing positive treatment response as defined by a rating of 1 or 2 (very much/much improved) on the CGI-I, showed a significantly greater treatment response with ERP at 3 months (36% [95% CI 26-45], n=101) than for psychoeducation (20% [95% CI 12-28], n=100), OR 2·22 (95% CI: 1·17 to 4·20). This superior treatment response was sustained at 6 months for ERP (47% [95% CI 37- 57], n=93) compared to psychoeducation (29% [95% CI 20-39], n=93), OR 2·20 (95% CI: 1·20 to 4·04). Table 3 shows there was a higher number of responders at both time points in the ERP group.

Two serious adverse events (SAE) were recorded during the trial, affecting two participants who were both in the psychoeducation group. Both SAEs were reviewed by the independent TSC and DMC and deemed unrelated to trial participation. The SAEs included a male participant collapsing and being hospitalised which was found to be due to a functional

movement disorder and a female participant attending accident and emergency due to a tic-attack. Both participants were discharged from hospital with no further action. The parents stated they did not feel the events had been bought on by ORBIT trial participation and participants had not been recently engaging with the internet-delivered content when the events occurred. There were slightly fewer AEs in the ERP group compared to psychoeducation (359 vs 431) and fewer participants in the ERP group experienced one or more adverse events (n=88/112; 79%) than in the psychoeducation group (n=94/112; 84%). The most commonly occurring AEs were low mood, increased in tics and anger/irritability (see appendix p6 for further details).

Overall, engagement with the intervention was high in both groups, with minimum treatment completion (≥ 4 chapters) rates of 88% (99/112) in the ERP group and 94% (105/112) in the psychoeducation group. Similarly, number of log-ins were comparable across both groups, although a slightly higher number of log-ins for the participants in the ERP group (see appendix p7). Perception of treatment suitability and credibility were also high across both groups (see appendix p7). Approximately 15 minutes more therapist time was spent supporting the participants in the ERP group compared to the psychoeducation, however, therapist time required to effectively support the intervention was low at approximately 2·5 hours contact time per participant, approximately 15 minutes per week (combined child/young person and parent/carer contact time).

The fixed yearly cost of delivering the intervention was £103·64 per participant (calculated on £8494 yearly cost of the BIP platform and total cost of supervision and training at £14719·78). As both interventions were delivered on the same platform there was no difference in fixed costs.

A variable cost was also calculated at £0·17 for each time a participant or one of their parents logged in to account for the SMS notification. Table 4 shows there was a small but significant difference between the two groups in the variable costs of the platform resulting from more platform logins and slightly more therapist contact time in the ERP intervention group (see appendix p14-15 and table 4). There were no significant differences in wider health care costs (see appendix). Combining fixed and variable costs and including wider health care costs delivering the ERP intervention cost £159 (95% CI -£-£53 to £370), per participant compared to the psychoeducation group.

DISCUSSION

To our knowledge, ORBIT is the first adequately-powered, randomised, controlled trial of ERP for tics. ORBIT also represents the largest trial of any behavioural treatment for tics and the first trial to examine the effectiveness of an online internet-delivered behavioural intervention for tics in children and adolescents compared to an active control condition. The results support the clinical effectiveness of online delivery of therapist-supported ERP for tics. The trial recruited ahead of time and target, reflecting a significant unmet treatment need in the population. Retention to the primary outcome at the primary endpoint (90%) and 6-month follow-up (>80%) were excellent. Acceptability and safety of the intervention was high. Analysis of our primary outcome (tic severity at 3 months post-randomisation) indicated a significant effect in favour of therapist-supported ERP compared to supported psychoeducation. Importantly, the therapeutic effect was durable and slightly increased at 6-months follow-up. Compared with the psychoeducation comparator, participants were twice as likely to show a positive treatment response with the ERP intervention with just under half (47%) having responded positively by 6-month follow-up.

The participants in this trial had a moderate to severe level of baseline tic severity (mean YGTSS-TTSS 28·4 SD 7·7), which is approximately half a standard deviation higher than reported in previous face-to-face behavioural treatment trials.[2,5] The trial design minimised the clinical comorbidity exclusions, resulting in a sample broadly representative of real-world clinical practice, and included participants with autism spectrum disorder (ASD), a group usually excluded in similar behavioural intervention trials. In the behavioural intervention group, just under one third had a co-existing anxiety disorder and just under one quarter had ADHD. The reduction in tics associated with the behavioural intervention was similar in those with and without co-existing anxiety and ADHD diagnoses. A relatively small proportion of participants (13%) were concurrently receiving tic medication. A particular strength of the design was the inclusion of an active comparator arm controlling for non-specific effects of therapist contact, homework assignments, and online access. The uptake of both the ERP and psychoeducation was excellent.

In our previous systematic review of tic treatments in children and adolescents,[2] we identified two superiority trials of face-to-face behavioural therapy (HRT/CBIT) for tics (N = 133) with evidence of a medium-sized effect in improving tics in favour of behavioural therapy (HRT/CBIT) when compared to waitlist/supportive psychotherapy (pooled effect size 0·64; 95% CI 0·29-0·99).[2,4] The magnitude of effect of this online ERP is about half the size reported from previous superiority trials of face-to-face HRT/CBIT for tics.[2] However, it is difficult to make direct comparisons of therapeutic efficacy with previous trials of face-to-face behavioural therapy given that this trial had a higher level of baseline tic severity, fewer co-morbidity exclusions, a lower proportion of participants receiving tic medication, longer follow-up and a potent active comparator. In practice, the direct comparison of efficacy may also be misleading with respect to implementation because the purpose is not to replace face-to-face therapy, but to allow this scare resource to be better targeted to those who need it

most and to offer an effective digitally enabled intervention to a much larger population of children/adolescents who are currently unable to access any behavioural treatment for tics.

A major difference between online delivery and face-to-face behavioural therapy for tics is the reduced amount of therapist time, required skill level of the therapist and cost. The total therapist contact time in the current trial was around 2·5 hours compared to 9-10 hours in comparable evidence-based face-to-face behavioural therapy for tics. Given the shortage of highly trained therapists with expertise in tic disorders and limited access to behavioural therapy, online delivery of ERP for tics has the potential to greatly expand the reach of effective behavioural interventions. From a public health perspective, with more efficient use of therapist time it should be possible to treat four people for every one person treated with face-to-face therapy. In addition, the requirement for less experienced therapists to support online behavioural therapy should expand the potential pool of therapists and thereby further extend the availability of online delivered behavioural therapy for tics. A further strength of the online delivery model is that fidelity of therapeutic content is built into the intervention, making transfer to real-world effectiveness much less susceptible than in traditional face-to-face therapy to therapeutic drift and the skill level of individual therapists.

The study has a number of limitations. First, despite being the largest trial to date of a behavioural intervention for tics, it is also the first adequately powered trial of therapist-supported, online ERP and further replications are required. Second, it is not possible in this trial to separate the effects of digital online delivery and ERP. In future, clinical- and cost-effectiveness comparisons of digital online vs. face-to-face ERP/CBIT will be needed. Third, there remains the question of the ‘digital divide’ whereby some people do not have sufficient access to the Internet and smartphones. This could have potentially limited the reach of this internet-delivered ERP intervention. While this does not appear to be an issue in the UK with 90% of households having access to the Internet and 98% of young people owning a

smartphone according to the Office for National Statistics,[32] it may be an important consideration when generalising these findings to other countries, or vulnerable groups, with lower levels of online access. Fourth, whilst the sex distribution is typical for a tic disorder population, a large proportion of the sample was white, which may limit the generalisability of the findings with regards to ethnicity. Fifth, the level of tic medication use and co-morbid obsessive compulsive disorder (OCD) diagnoses were lower than in comparable studies conducted in the United States, which may limit generalisability to these populations. Finally, while the level of tic severity in ORBIT is higher than in comparable studies, the findings may not be generalisable to those young people with tics outside the severity range of this study population.

Although a full economic evaluation of the intervention was conducted, the limited follow-up duration of 6-months meant that a meaningful incremental cost per QALY analysis in line with guidance could not be conducted as it would not capture the full benefits of the intervention. A further naturalistic follow-up of this trial to 18-months (Phase 2) is being conducted which will be used to calculate cost and QALYs over a longer time horizon. Further implementation research will also be required to determine how best to integrate online behavioural therapy for tics within treatment pathways. For example, digital/online delivery may work best as a first-line behavioural intervention with non- or poor responders being 'stepped-up' to more intensive face-to-face therapy. A further model to evaluate would be the 'blending' of online and face-to-face therapy for more complex cases, thereby reducing the overall number of face-to-face sessions required.

While an economic evaluation including QALYs is required to provide comparable evidence of cost-effectiveness, evidence from this trial suggests that implementation of online therapist-supported ERP has a high probability of cost-effectiveness for reduction in tic

symptoms, with a non-significant increase in costs, and the potential to greatly increase the availability of effective behavioural treatment for children and adolescents with tic disorders.

RESEARCH IN CONTEXT PANEL

Evidence before this study:

In 2016 we conducted a systematic review of interventions for children and adolescents with tic disorders. Twenty-one databases covering medical/health (e.g. Medline, CENTRAL, PsycINFO), education (e.g. ERIC), social care (e.g. Social Services Abstracts) and grey literature (e.g. Health Management Information Consortium) topics were searched for studies in any language. Searches were conducted from database inception to 1st January 2013 and updated in October 2014. The search strategy included key words (tic or tics or tourette$) and relevant subject headings. This search identified two randomised controlled trials (RCTs) of habit reversal training (HRT)/comprehensive behavioural intervention (CBIT) (SMD = 0.64; 95% CI 0.99-0.29; N = 133). In 2020, we updated this search using the same inclusion criteria and found no new trials of behavioural interventions for tics in children and adolescents. In 2017, we conducted a meta-review of scoping, narrative, systematic or meta-analytical reviews investigating the effectiveness of digital health interventions (DHIs) for mental health problems in children and adolescents. We also updated a systematic review of randomised controlled trials (RCTs) of DHIs for CYP published in the previous 3 years. The search was run on 11 online databases (Allied and Complementary Medicine, Ovid, MEDLINE, PsychINFO, PsychARTICLES, Embase, PubMed, ASSIA, Cochrane Library, CINAHL and Web of Science), and a limited keyword search was also performed on the JMIR Publications database. The search identified 30 unique RCTs of digital health interventions, with no digital intervention studies identified that focussed on treatment of tic disorders.

We have previously reported that only one in five children and adolescents in the UK have access to structured behavioural interventions for tics, and of these, less than half receive a minimum effective dose of therapy. Widely accessible and effective online behavioural interventions for tics are urgently needed.

Added value of this study:

This is the first RCT, to our knowledge, that reports the clinical efficacy, safety and costs of therapist and parent-supported online Exposure and Response Prevention (ERP) behavioural therapy for tics in children aged 9 to 17 years. We demonstrated that this 10-week online ERP intervention was highly acceptable, well tolerated, and effective in reducing tics. The magnitude of the effect on tic reduction was durable with a slightly greater effect 3 months after treatment ended (6-month follow-up). Approximately a quarter of the therapist contact time is required compared to face-to-face behaviour therapy.

Implications of all the available evidence:

Data from this trial supports the efficacy of ERP for tics. Implementation of digitally enabled ERP for tics is an efficient public mental health approach to increase the population reach of an effective treatment for children and adolescents with tic disorders. Further research is needed to determine the optimum care pathways with respect to sequencing and integration of digital and face-to-face behavioural therapy for tics in children and adolescents.

Contributors

CH was the chief investigator and conceived the study. The study design was conceived and written by CH, CLH, PA, TM, DM-C, EM, LM, IH, ES, RJ, RH, and CG. CLH wrote the trial protocol with input from all co-authors. CH, CLH, EM, SB, TM, CS, BJB were responsible for study implementation and general project management. BJB, CS, KK, CM were responsible for recruitment and follow-ups. TM and JK provided therapist supervision. LRC, EBD, AE, NK were the trial therapists. CLH oversaw trial management. LM and RJ designed and wrote the statistical analysis plan. RJ and LM conducted the analysis. RH designed the economic evaluation; RH and MLN wrote the health economic analysis plan. MLN and RH conducted the economic evaluation. CLH and CH drafted the original manuscript. All authors contributed to the interpretation of the data and re-drafts. All authors had full access to the study data and take responsibility for the integrity and accuracy of the data and accept responsibility for publication. CH is guarantor.

Declaration of interests

All authors have completed the ICMJE uniform disclosure from. Aside from receiving funding from NIHR to support their salaries CLH, LM, EBD, RJ, KK, BJB, CS, CM, ES, PA, TM, IH, JK, RH, MLN, AE, LRC, NK, SB, CG, EM declare no conflict of interests. CH declares he was Principal Investigator on a grant from the National Institute of Health Research (NIHR) Health Technology Assessment programme to conduct an Evidence Synthesis on the treatments for tics and Tourette syndrome in children and young people' HTA Project:10/142/01. DM-C reports personal fees from Elsevier, personal fees from UpToDate Inc. outside the submitted work.

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Data sharing agreement

Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, data dictionary and appendices) will be available. Study protocol, statistical analysis plan, informed consent form, patient information sheets will also be available beginning 3 months and ending 5 years following article publication. Researchers who provide a methodologically sound proposal should direct these to priment@ucl.ac.uk to gain access, data requestors will need to sign a data access agreement.

REFERENCES

1. Hollis C, Pennant M, Cuenca J, et al. Clinical effectiveness and patient perspectives of different treatment strategies for tics in children and adolescents with Tourette syndrome: a systematic review and qualitative analysis. *Health Technol Asses* 2016; **20**(4): 1-450.
2. Whittington C, Pennant M, Kendall T, et al. Practitioner Review: Treatments for Tourette syndrome in children and young people–a systematic review. *J Child Psychol Psyc* 2016; **57**(9): 988-1004.
3. Piacentini J, Woods DW, Scahill L, et al. Behavior therapy for children with Tourette disorder: a randomized controlled trial. *JAMA* 2010; **303**(19): 1929-37.
4. Wilhelm S, Peterson AL, Piacentini J, et al. Randomized Trial of Behavior Therapy for Adults With Tourette Syndrome. *Arch Gen Psychiatry*. 2012; **69**(8):795–803.
5. Verdellen CW, Keijsers GP, Cath DC, Hoogduin CA. Exposure with response prevention versus habit reversal in Tourettes's syndrome: a controlled study. *Behav Res Ther* 2004; **42**(5): 501-11.

6. Cuenca J, Glazebrook C, Kendall T, et al. Perceptions of treatment for tics among young people with Tourette syndrome and their parents: a mixed methods study. *BMC Psychiatry* 2015; **15**(1): 46.

7. Torous J, Myrick KJ, Rauseo-Ricupero N, Firth J. Digital mental health and COVID-19: Using technology today to accelerate the curve on access and quality tomorrow. *JMIR Mental Health* 2020; **7**(3): e18848.

8. Andersson G, Titov N, Dear BF, Rozental A, Carlbring P. Internet-delivered psychological treatments: from innovation to implementation. *World Psychiatry* 2019; **18**(1): 20-8.

9. Palmqvist B, Carlbring P, Andersson G. Internet-delivered treatments with or without therapist input: does the therapist factor have implications for efficacy and cost? *Expert Rev Pharm Out* 2007; **7**(3): 291-7.

10. Pennant ME, Loucas CE, Whittington C, et al. Computerised therapies for anxiety and depression in children and young people: a systematic review and meta-analysis. *Behaviour Research and Therapy* 2015; **67**: 1-18.

11. Lenhard F, Vigerland S, Andersson E, et al. Internet-delivered cognitive behavior therapy for adolescents with obsessive-compulsive disorder: an open trial. *PLoS One* 2014; **9**(6): e100773.

12. Vigerland S, Ljótsson B, Thulin U, Öst L-G, Andersson G, Serlachius E. Internet-delivered cognitive behavioural therapy for children with anxiety disorders: A randomised controlled trial. *Behav Res Ther* 2016; **76**: 47-56.

13. Hollis C, Falconer CJ, Martin JL, et al. Annual Research Review: Digital health interventions for children and young people with mental health problems–a systematic and meta-review. *J Child Psychol Psyc* 2017; **58**(4): 474-503.

14. Andrén P, Aspvall K, de la Cruz LF, et al. Therapist-guided and parent-guided internet-delivered behaviour therapy for paediatric Tourette's disorder: a pilot randomised controlled trial with long-term follow-up. *BMJ Open* 2019; **9**(2): e024685.

15. Hall C, Davies E, Andrén P, et al. Investigating a therapist-guided, parent-assisted remote digital behavioural intervention for tics in children and adolescents—'Online Remote Behavioural Intervention for Tics'(ORBIT) trial: protocol of an internal pilot study and single-blind randomised controlled trial. *BMJ Open* 2019; **9**(1): e027583.

16. Leckman JF, Riddle MA, Hardin MT, et al. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. *Journal of the American Academy of Child & Adolescent Psychiatry* 1989; **28**(4): 566-73.

17. Goodman R, Ford T, Richards H, Gatward R, Meltzer H. The development and well-being assessment: Description and initial validation of an integrated assessment of child and adolescent psychopathology. *Journal of Child Psychology and Psychiatry* 2000; **41**(5): 645-55.

18. McKenzie K, Murray GC, Murray AL. The Validity of the Child and Adolescent Intellectual Disability Screening Questionnaire (CAIDS-Q) with children aged 6–7 years, 11 months: A brief report. *Psychiat Res* 2013; **210**(2): 675-7.

19. Byford S, Barrett B, Roberts C, et al. Cost-effectiveness of selective serotonin reuptake inhibitors and routine specialist care with and without cognitive–behavioural therapy in adolescents with major depression. *Brit J Psychiat* 2007; **191**(6): 521-7.

20. Shaffer D, Gould MS, Brasic J, et al. A children's global assessment scale (CGAS). *Arch Gen Psychiat* 1983; **40**(11): 1228-31.

21. Verdellen C, Van De Griendt J, Kriens S, Van Oostrum I. Tics - Therapist Manual. Amsterdam: Boom Publishers; 2011.

22. Chamberlain LR, Hall CL, Andrén P, et al. Therapist-Supported Online Interventions for Children and Young People With Tic Disorders: Lessons Learned From a Randomized Controlled Trial and Considerations for Future Practice. *JMIR Mental Health* 2020; **7**(10): e19600.

23. Guy W. ECDEU assessment manual for psychopharmacology. *US Department of Health, and Welfare* 1976: 534-7.

24. Goodman R. The extended version of the Strengths and Difficulties Questionnaire as a guide to child psychiatric caseness and consequent burden. *Journal of Child Psychology and Psychiatry* 1999; **40**(5): 791-9.

25. Stevens K. The Child Health Utility 9D (CHU9D). *A new, paediatric, preference-based measure of health related quality of life PRO Newsletter* 2010; **43**: 11-2.

26. Hill P, Taylor E. An auditable protocol for treating attention deficit/hyperactivity disorder. *Arch Dis Child* 2001; **84**(5): 404-9.

27. Chang S, Himle MB, Tucker BT, Woods DW, Piacentini J. Initial psychometric properties of a brief parent-report instrument for assessing tic severity in children with chronic tic disorders. *Child Fam Behav Ther* 2009; **31**(3): 181-91.

28. Cavanna AE, Luoni C, Selvini C, et al. Disease-specific quality of life in young patients with Tourette syndrome. *Pediatr Neurol* 2013; **48**(2): 111-4.

29. Angold A, Costello EJ, Messer SC, Pickles A. Development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. *Int J Meth Psych Res* 1995.

30. Spence SH. A measure of anxiety symptoms among children. *Behav Res Ther* 1998; **36**(5): 545-66.

31. Woods DW, Piacentini J, Himle MB, Chang S. Premonitory urge for tics scale (PUTS): Initial psychometric results and examination of the premonitory urge phenomenon in youths with tic disorders. *J Dev Behav Pediatr* 2005; 26:397–403.

32. Office for National Statistics. Exploring the UK's digital divide. [Internet]. 2019 [cited 2021 June 4] .Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/householdcharacteristics/homeinternetandsocialmediausage/articles/exploringtheuksdigitaldivide/2019-03-04

Tables

Table 1. Baseline characteristics of participants

	Psychoeducation (N = 112) N (%)	**ERP (N = 112)** N (%)
Age at randomisation (years) – Mean (SD)	12.4 (2.1)	12.2 (2.0)
Sex		
Male	87 (78%)	90 (80%)
Female	25 (22%)	22 (20%)
Ethnicity		
White	99 (88%)	96 (86%)
Asian	3 (3%)	7(6%)
Black	0 (0%)	1(1%)
Mixed	7 (6%)	3 (3%)
Other	1 (1%)	0 (0%)
Not given	2 (2%)	5 (4%)
Main caregiver in trial		
Mother	101 (90%)	93 (83%)
Father	10 (9%)	16 (14%)
Grandmother	1 (1%)	1 (1%)
Other	0 (0%)	2 (2%)
Mother's highest educational level		
No qualifications	1 (1%)	3 (3%)
Mandatory secondary education (eg. GCSEs)	17 (15%)	16 (14%)
Further education (eg. A levels, BTEC, NVQ)	32 (29%)	33 (29%)
Higher education (eg. BA, BSc)	46 (41%)	46 (41%)
Postgraduate education (eg, MA, MSc, PhD)	16 (14%)	14 (13%)
Father's highest educational level		
No qualifications	5 (4%)	2 (2%)
Mandatory secondary education (eg. GCSEs)	29 (26%)	29 (26%)
Further education (eg. A levels, BTEC, NVQ)	33 (29%)	35 (31%)
Higher education (eg. BA, BSc)	34 (30%)	32 (29%)
Postgraduate education (eg, MA, MSc, PhD)	11 (9%)	14 (13%)
Mother's occupational status		

Not in work/ unemployed	22 (20%)	19 (20%)
Lower occupational status $	26 (23%)	24 (21%)
Higher occupational status $$	57 (51%)	65 (58%)
Other	7 (6%)	4 (4%)
Father's occupational status		
Not in work/ unemployed	4 (4%)	2 (2%)
Lower occupational status $	30 (27%)	33 (29%)
Higher occupational status $$	67 (60%)	65 (58%)
Other	10 (9%)	12 (11%)
Tic typology		
Both motor and vocal tics	106 (95%)	103 (92%)
Motor tics only	6 (5%)	9 (8%)
Vocal tics only	0 (0%)	0 (0%)
Comorbidities		
Anxiety disorder	27 (24%)	34 (30%)
Attention deficit hyperactivity disorder (ADHD)	25 (22%)	26 (23%)
Oppositional defiant disorder (ODD)	23/111 (21%)	26/110 (24%)
Autism spectrum disorders	4/112 (4%)	9/111 (8%)
Obsessive compulsive disorder (OCD)	3 (3%)	8 (7%)
Major depression	6 (5%)	2 (2%)
Conduct disorder	2/111 (2%)	3/110 (3%)
Taking any tic medication*	16 (13%)	14 (13%)
Centre		
Nottingham	57 (51%)	57 (51%)
London	55 (49%)	55 (49%)

***Notes**: Statistics are n (%) unless otherwise specified. SD = standard deviation. Percentages are given to the nearest whole number. Comorbidities are based on >=50% probability of having a DSM-IV / DSM 5 diagnosis as assessed by the Development and Wellbeing Assessment (DAWBA). Anxiety disorders include separation anxiety, specific phobias, social phobia, panic disorder, agoraphobia and post traumatic stress disorder (PTSD). Diagnoses are not mutually exclusive and so percentages are not expected to total 100%. Denominators for percentages for comorbidities are not always the full sample, because insufficient information was supplied for some participants to make either a positive or negative diagnosis. *Any tic medication included: Clonidine, Risperidone, Aripiprazole, Haloperidol, Guanfacine, Topiramate. $Lower occupational statuses are defined as manual or semi-manual occupations. $$Higher occupational statuses are defined as professional occupations. ERP = exposure and response prevention.*

***Table 2*. Primary and secondary outcomes at all time points**

	Psychoeducation Mean (SD)	**ERP** Mean (SD)	**Estimated difference (95% CI)**	**Standardised effect size**
Baseline	**(N = 112)**	**(N = 112)**		
Primary outcome				
Total Tic Severity Score (TTSS) on the Yale Global Tic Severity Scale (YGTSS)	28·4 (7·1)	28·4 (7·7)		
Secondary outcomes				
Impairment score on the Yale Global Tic Severity Scale (YGTSS)	22·9 (9·9)	23·8 (10·3)		
Parent Tic Questionnaire (PTQ)	53·1 (26·1)	54·7 (29·9)		
Children's Global Assessment Scale (CGAS)	72·1 (11·8)	70·7 (13·7)		
Strengths and Difficulties Questionnaire (SDQ)	16·3 (6·2)	18·0 (6·5)		
Mood and Feelings Questionnaire (MFQ)	15·9 (11·5)	16·3 (11·3)		
Spence Child Anxiety Scale (SCAS)	30·5 (17·9)	32·9 (20·2)		
Child and Adolescent Gilles de la Tourette Syndrome–Quality of Life Scale (C&A-GTS-QOL)	35·0 (17·2)	36·6 (16·4)		
3 months				
Primary outcome				
Total Tic Severity Score (TTSS) on the Yale Global Tic Severity Scale (YGTSS)	26·8 (7·3)	23·9 (8·2)	-2·29 (-3·86 to -0·71)	-0·31 (-0·52 to -0·10)
Secondary outcomes				
Impairment score on the Yale Global Tic Severity Scale (YGTSS)	19·1 (10·9)	16·7 (10·4)	-2·24 (-4·82 to 0·33)	
Parent Tic Questionnaire (PTQ)	45·7 (25·5)	34·7 (26·4)	-9·44 (-15·37 to -3·51)	
Clinical Global Impression Scale – Improvement (CGI-I)	3·37 (1·11)	2·96 (1·1)	-0·41 (-0·71 to -0·11)	
Children's Global Assessment Scale (CGAS)	75·2 (12·6)	75·9 (12·6)	0·96 (-1·48 to 3·41)	
Strengths and Difficulties Questionnaire (SDQ)	14.2 (6.3)	14.7 (6.1)	-0·38 (-1.62 to 0.85)	
Mood and Feelings Questionnaire (MFQ)	12.6 (11.1)	10.7 (11.1)	-1·36 (-3·75 to 1·02)	
Spence Child Anxiety Scale (SCAS)	28.2 (18.3)	27.2 (19.0)	-2·80 (-6·52 to 0·93)	

Child and Adolescent Gilles de la Tourette Syndrome–Quality of Life Scale (C&A-GTS-QOL)	31.8 (17.7)	25.7 (18.0)	-4·81 (-8·79 to -0·83)	
6 months				
Primary outcome				
Total Tic Severity Score (TTSS) on the Yale Global Tic Severity Scale (YGTSS)	25·0 (7·6)	21·5 (8·8)	-2·64 (-4·56 to -0·73)	-0·36 (-0·62 to -0·10)
Secondary outcomes				
Impairment score on the Yale Global Tic Severity Scale (YGTSS)	17·0 (10·5)	14·7 (10·7)	-1·95 (-4·68 to 0·78)	
Parent Tic Questionnaire (PTQ)	40·6 (24·3)	31·1 (21·6)	-8·60 (-14·43 to -2·77)	
Clinical Global Impression Scale – Improvement (CGI-I)	3·1 (1·1)	2·8 (1·3)	-0·31 (-0·66 to 0·03)	
Children's Global Assessment Scale (CGAS)	76·8 (12·3)	77·5 (14·7)	0·60 (-2·24 to 3·44)	
Strengths and Difficulties Questionnaire (SDQ)	13·3 (6·1)	15·3 (6·2)	0·57 (-0·93 to 2·07)	
Mood and Feelings Questionnaire (MFQ)	11·4 (11·2)	11·4 (12·1)	-0·61 (-3·85 to 2·64)	
Spence Child Anxiety Scale (SCAS)	25·9 (18·7)	25·7 (19·6)	-5·10 (-9·70 to -0·50)	
Child and Adolescent Gilles de la Tourette Syndrome–Quality of Life Scale (C&A-GTS-QOL)	28·9 (18·3)	27·4 (16·5)	-2·91 (-7·60 to 1·78)	

***Notes**: Statistics are mean (SD) unless otherwise specified and are calculated for all available data. SD = standard deviation. Higher scores on the C&A-GTS-QOL indicate **worse** quality of life. There was 1 missing value for the SCAS scale at baseline. All other measures were complete. ERP = exposure and response prevention. Statistical models adjusted for the baseline measure of the outcome in question (with the exception of the CGI-I) and site. For the standardised effect size, YGTSS-TTSS was standardised by the pooled mean and SD at baseline. At 3 months follow up, there were 12 missing observations (11%) for the primary outcome in the ERP arm compared to 11 (10%) in the psychoeducation arm. The quantity of missing data for secondary outcomes was similar in both trial arms.*

Table 3. **Response to treatment at 3 and 6 months follow-up**

	Psychoeducation N (%)	**ERP** N (%)	**Odds ratio (95% CI)**
3 months	**(N = 100)**	**(N = 101)**	
CGI-I scored indicating 'much' or 'very much' improved (responded to treatment)	20 (20%)	36 (36%)	2.22 (1·17 to 4·20)
6 months	**(N=93)**	**(N=93)**	
CGI-I scored indicating 'much' or 'very much' improved (responded to treatment)	27 (29%)	44 (47%)	2.20 (1.20 to 4.04)
Change in response between 3 and 6 months	**(N=93)**	**(N=90)**	
No response to treatment at either time	56 (60%)	37 (41%)	
Response at both time	9 (10%)	23 (26%)	
New responder at 6 months	18 (19%)	20 (22%)	
Relapsed responder at 6 months	10 (11%)	10 (11%)	

Notes*: Statistics are frequency (N) and percentage (%) unless otherwise specified. CGI-I = Clinical Global Impressions – Improvement. CI = confidence interval. Statistical models adjusted for site. ERP = exposure and response prevention.*

***Table 4*. Comparison of variable costs between the psychoeducation (control) and ERP (intervention) group across the 6 months**

	Psychoeducation (Control) (N = 111)	**ERP (Intervention) (N = 111)**	**Difference at 6 months £ (95% CI)**
	Mean (SD) £	Mean (SD) £	
Cost of therapist contact time			
Young person	16 (9)	18 (9)	
Parent/ carer 1	22 (10)	25 (13)	
Parent/ carer 2	0·09 (0·56)	0·20 (2)	
Total	38 (17)	43 (20)	4·99* (0·01 to 9·96)
Login costs			
Young person	3 (1)	3 (2)	
Parent/ carer 1	3 (2)	3 (2)	
Parent/ carer 2	0·01 (0·10)	0·04 (0·33)	
Total	6 (3)	7 (4)	1·25* (0·46 to 2·04)
Total variable costs	44 (18)	50 (22)	6·27 (0·88 to 11·67)

***Note:** *Indicates statistically significant. CI = confidence interval. ERP =exposure and response prevention.*

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Tic typology		
Both motor and vocal tics	106 (95%)	103 (92%)
Motor tics only	6 (5%)	9 (8%)
Vocal tics only	0 (0%)	0 (0%)
Comorbidities		
Anxiety disorder	27 (24%)	34 (30%)
Attention deficit hyperactivity disorder (ADHD)	25 (22%)	26 (23%)
Oppositional defiant disorder (ODD)	23/111 (21%)	26/110 (24%)
Autism spectrum disorders	4/112 (4%)	9/111 (8%)
Obsessive compulsive disorder (OCD)	3 (3%)	8 (7%)
Major depression	6 (5%)	2 (2%)
Conduct disorder	2/111 (2%)	3/110 (3%)
Taking any tic medication*	16 (13%)	14 (13%)
Centre		
Nottingham	57 (51%)	57 (51%)
London	55 (49%)	55 (49%)

***Notes**: Statistics are n (%) unless otherwise specified. SD = standard deviation. Percentages are given to the nearest whole number. Comorbidities are based on >=50% probability of having a DSM-IV / DSM 5 diagnosis as assessed by the Development and Wellbeing Assessment (DAWBA). Anxiety disorders include separation anxiety, specific phobias, social phobia, panic disorder, agoraphobia and post traumatic stress disorder (PTSD). Diagnoses are not mutually exclusive and so percentages are not expected to total 100%. Denominators for percentages for comorbidities are not always the full sample, because insufficient information was supplied for some participants to make either a positive or negative diagnosis. *Any tic medication included: Clonidine, Risperidone, Aripiprazole, Haloperidol, Guanfacine, Topiramate. $Lower occupational statuses are defined as manual or semi-manual occupations. $$Higher occupational statuses are defined as professional occupations. ERP = exposure and response prevention.*

***Table 2*. Primary and secondary outcomes at all time points**

	Psychoeducation Mean (SD)	**ERP** Mean (SD)	**Estimated difference (95% CI)**	**Standardised effect size**
Baseline	**(N = 112)**	**(N = 112)**		
Primary outcome				
Total Tic Severity Score (TTSS) on the Yale Global Tic Severity Scale (YGTSS)	28·4 (7·1)	28·4 (7·7)		
Secondary outcomes				
Impairment score on the Yale Global Tic Severity Scale (YGTSS)	22·9 (9·9)	23·8 (10·3)		
Parent Tic Questionnaire (PTQ)	53·1 (26·1)	54·7 (29·9)		
Children's Global Assessment Scale (CGAS)	72·1 (11·8)	70·7 (13·7)		
Strengths and Difficulties Questionnaire (SDQ)	16·3 (6·2)	18·0 (6·5)		
Mood and Feelings Questionnaire (MFQ)	15·9 (11·5)	16·3 (11·3)		
Spence Child Anxiety Scale (SCAS)	30·5 (17·9)	32·9 (20·2)		
Child and Adolescent Gilles de la Tourette Syndrome–Quality of Life Scale (C&A-GTS-QOL)	35·0 (17·2)	36·6 (16·4)		
3 months				
Primary outcome				
Total Tic Severity Score (TTSS) on the Yale Global Tic Severity Scale (YGTSS)	26·8 (7·3)	23·9 (8·2)	-2·29 (-3·86 to -0·71)	-0·31 (-0·52 to -0·10)
Secondary outcomes				
Impairment score on the Yale Global Tic Severity Scale (YGTSS)	19·1 (10·9)	16·7 (10·4)	-2·24 (-4·82 to 0·33)	
Parent Tic Questionnaire (PTQ)	45·7 (25·5)	34·7 (26·4)	-9·44 (-15·37 to -3·51)	

Clinical Global Impression Scale – Improvement (CGI-I)	3·37 (1·11)	2·96 (1·1)	-0·41 (-0·71 to -0·11)	
Children's Global Assessment Scale (CGAS)	75·2 (12·6)	75·9 (12·6)	0·96 (-1·48 to 3·41)	
Strengths and Difficulties Questionnaire (SDQ)	14.2 (6.3)	14.7 (6.1)	-0·38 (-1.62 to 0.85)	
Mood and Feelings Questionnaire (MFQ)	12.6 (11.1)	10.7 (11.1)	-1·36 (-3·75 to 1·02)	
Spence Child Anxiety Scale (SCAS)	28.2 (18.3)	27.2 (19.0)	-2·80 (-6·52 to 0·93)	
Child and Adolescent Gilles de la Tourette Syndrome–Quality of Life Scale (C&A-GTS-QOL)	31.8 (17.7)	25.7 (18.0)	-4·81 (-8·79 to -0·83)	
6 months				
Primary outcome				
Total Tic Severity Score (TTSS) on the Yale Global Tic Severity Scale (YGTSS)	25·0 (7·6)	21·5 (8·8)	-2·64 (-4·56 to -0·73)	-0·36 (-0·62 to -0·10)
Secondary outcomes				
Impairment score on the Yale Global Tic Severity Scale (YGTSS)	17·0 (10·5)	14·7 (10·7)	-1·95 (-4·68 to 0·78)	
Parent Tic Questionnaire (PTQ)	40·6 (24·3)	31·1 (21·6)	-8·60 (-14·43 to -2·77)	
Clinical Global Impression Scale – Improvement (CGI-I)	3·1 (1·1)	2·8 (1·3)	-0·31 (-0·66 to 0·03)	
Children's Global Assessment Scale (CGAS)	76·8 (12·3)	77·5 (14·7)	0·60 (-2·24 to 3·44)	
Strengths and Difficulties Questionnaire (SDQ)	13·3 (6·1)	15·3 (6·2)	0·57 (-0·93 to 2·07)	
Mood and Feelings Questionnaire (MFQ)	11·4 (11·2)	11·4 (12·1)	-0·61 (-3·85 to 2·64)	
Spence Child Anxiety Scale (SCAS)	25·9 (18·7)	25·7 (19·6)	-5·10 (-9·70 to -0·50)	
Child and Adolescent Gilles de la Tourette Syndrome–Quality of Life Scale (C&A-GTS-QOL)	28·9 (18·3)	27·4 (16·5)	-2·91 (-7·60 to 1·78)	

***Notes**: Statistics are mean (SD) unless otherwise specified and are calculated for all available data. SD = standard deviation. Higher scores on the C&A-GTS-QOL indicate **worse** quality of life. There was 1 missing value for the SCAS scale at baseline. All other measures were complete. ERP = exposure and*

response prevention. Statistical models adjusted for the baseline measure of the outcome in question (with the exception of the CGI-I) and site. For the standardised effect size, YGTSS-TTSS was standardised by the pooled mean and SD at baseline. At 3 months follow up, there were 12 missing observations (11%) for the primary outcome in the ERP arm compared to 11 (10%) in the psychoeducation arm. The quantity of missing data for secondary outcomes was similar in both trial arms.

Table 3. **Response to treatment at 3 and 6 months follow-up**

	Psychoeducation N (%)	**ERP** N (%)	**Odds ratio (95% CI)**
3 months	**(N = 100)**	**(N = 101)**	
CGI-I scored indicating 'much' or 'very much' improved (responded to treatment)	20 (20%)	36 (36%)	2.22 (1·17 to 4·20)
6 months	**(N=93)**	**(N=93)**	
CGI-I scored indicating 'much' or 'very much' improved (responded to treatment)	27 (29%)	44 (47%)	2.20 (1.20 to 4.04)
Change in response between 3 and 6 months	**(N=93)**	**(N=90)**	
No response to treatment at either time	56 (60%)	37 (41%)	
Response at both time	9 (10%)	23 (26%)	
New responder at 6 months	18 (19%)	20 (22%)	
Relapsed responder at 6 months	10 (11%)	10 (11%)	

Notes*: Statistics are frequency (N) and percentage (%) unless otherwise specified. CGI-I = Clinical Global Impressions – Improvement. CI = confidence interval. Statistical models adjusted for site. ERP = exposure and response prevention.*

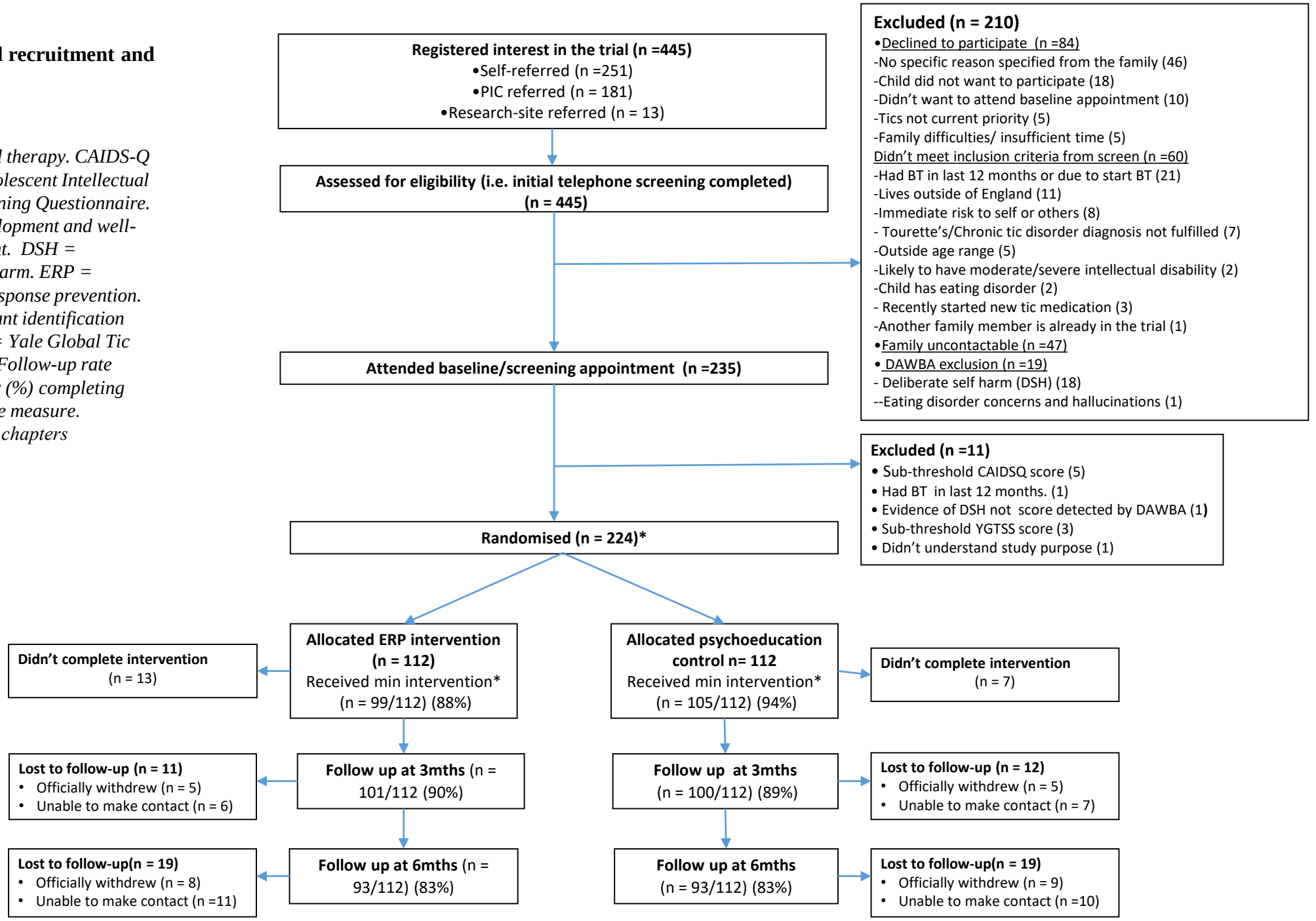
***Table 4*. Comparison of variable costs between the psychoeducation (control) and ERP (intervention) group across the 6 months**

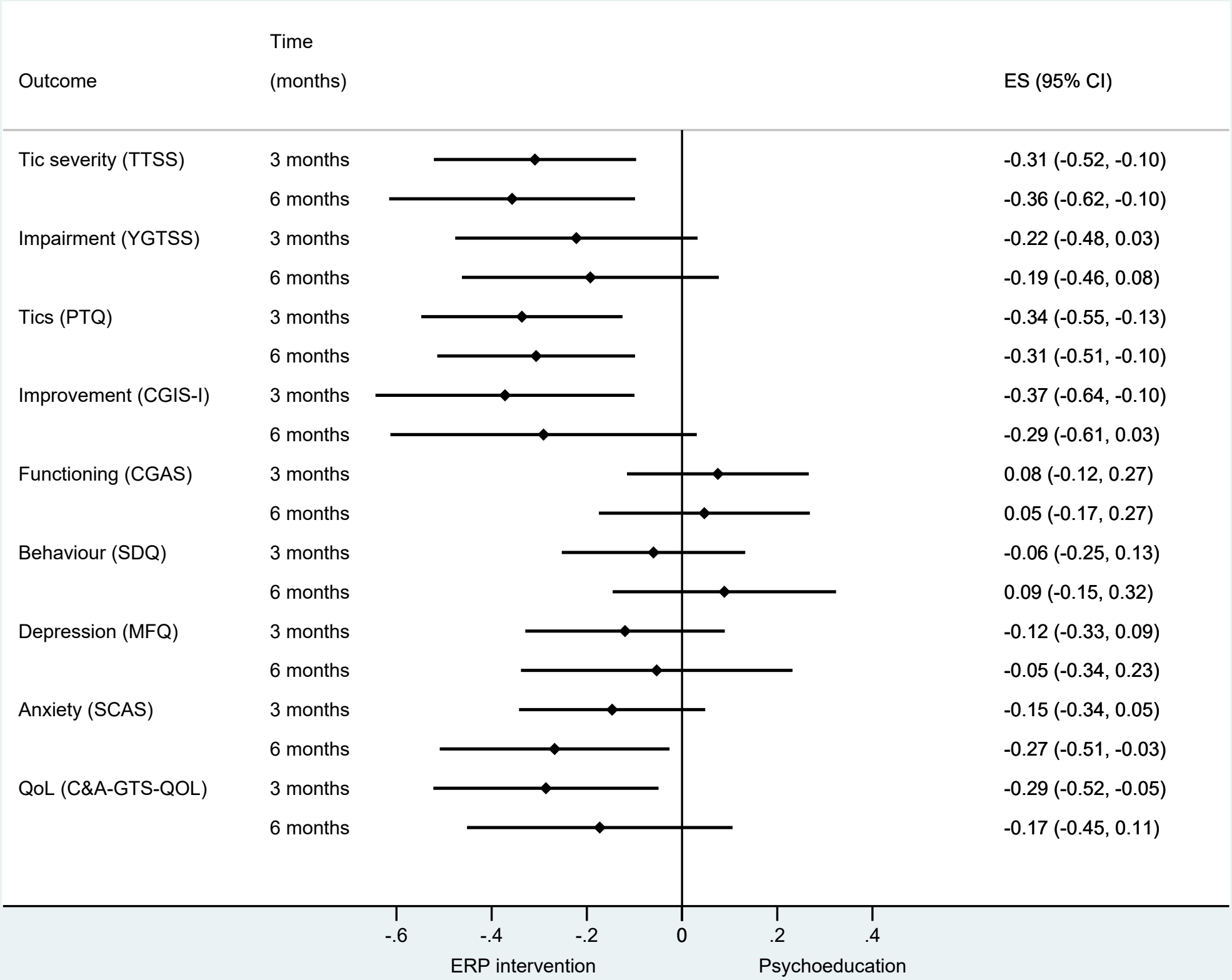
	Psychoeducation (Control) (N = 111)	**ERP (Intervention) (N = 111)**	**Difference at 6 months £ (95% CI)**
	Mean (SD) £	Mean (SD) £	
Cost of therapist contact time			
Young person	16 (9)	18 (9)	
Parent/ carer 1	22 (10)	25 (13)	
Parent/ carer 2	0·09 (0·56)	0·20 (2)	
Total	38 (17)	43 (20)	4·99* (0·01 to 9·96)
Login costs			
Young person	3 (1)	3 (2)	
Parent/ carer 1	3 (2)	3 (2)	
Parent/ carer 2	0·01 (0·10)	0·04 (0·33)	
Total	6 (3)	7 (4)	1·25* (0·46 to 2·04)
Total variable costs	44 (18)	50 (22)	6·27 (0·88 to 11·67)

***Note:* ****Indicates statistically significant. CI = confidence interval. ERP =exposure and response prevention.*

***Figure 1*. Trial recruitment and retention**

Note.
BT=behavioural therapy. CAIDS-Q = Child and Adolescent Intellectual Disability Screening Questionnaire. DAWBA = development and well-being assessment. DSH = deliberate self-harm. ERP = exposure and response prevention. PIC = participant identification centre. YGTSS = Yale Global Tic Severity Scale. Follow-up rate given as number (%) completing primary outcome measure.
** completed ≥ 4 chapters*




Outcome
Time (months)
ES (95% CI)
Tic severity (TTSS)
3 months
-0.31 (-0.52, -0.10)
6 months
-0.36 (-0.62, -0.10)
Impairment (YGTSS)
3 months
-0.22 (-0.48, 0.03)
6 months
-0.19 (-0.46, 0.08)
Tics (PTQ)
3 months
-0.34 (-0.55, -0.13)
6 months
-0.31 (-0.51, -0.10)
Improvement (CGIS-I)
3 months
-0.37 (-0.64, -0.10)
6 months
-0.29 (-0.61, 0.03)
Functioning (CGAS)
3 months
0.08 (-0.12, 0.27)
6 months
0.05 (-0.17, 0.27)
Behaviour (SDQ)
3 months
-0.06 (-0.25, 0.13)
6 months
0.09 (-0.15, 0.32)
Depression (MFQ)
3 months
-0.12 (-0.33, 0.09)
6 months
-0.05 (-0.34, 0.23)
Anxiety (SCAS)
3 months
-0.15 (-0.34, 0.05)
6 months
-0.27 (-0.51, -0.03)
QoL (C&A-GTS-QOL)
3 months
-0.29 (-0.52, -0.05)
6 months
-0.17 (-0.45, 0.11)
-.6
-.4
-.2
0
.2
.4
ERP intervention
Psychoeducation