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Long-term clinical and cost-effectiveness of a therapist-supported online remote behavioural intervention for tics in children and adolescents: extended 12- and 18-month follow-up of a single-blind randomised controlled trial

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Background: Little is known about the long-term effectiveness of behavioural therapy for tics. We aimed to assess the long-term clinical and cost-effectiveness of online therapist-supported exposure and response prevention (ERP) therapy for tics 12 and 18 months after treatment initiation. **Methods:** ORBIT (online remote behavioural intervention for tics) was a two-arm (1:1 ratio), superiority, single-blind, multicentre randomised controlled trial comparing online ERP for tics with online psychoeducation. The trial was conducted across two Child and Adolescent Mental Health Services in England. Participants were recruited from these two sites, across other clinics in England, or by self-referral. This study was a naturalistic follow-up of participants at 12- and 18-month postrandomisation. Participants were permitted to use alternative treatments recommended by their clinician. The key outcome was the Yale Global Tic Severity Scale Total Tic Severity Score (YGTSS-TTSS). A full economic evaluation was conducted. Registrations are ISRCTN (ISRCTN70758207); ClinicalTrials.gov (NCT03483493). **Results:** Two hundred and twenty-four participants were enrolled: 112 to ERP and 112 to psychoeducation. The sample was predominately male (177; 79%) and of white ethnicity (195; 87%). The ERP intervention reduced baseline YGTSS-TTSS by 2.64 points (95% CI: −4.48 to −0.79) with an effect size of −0.36 (95% CI: −0.61 to −0.11) after 12 months and by 2.01 points (95% CI: −3.86 to −0.15) with an effect size of −0.27 (95% CI -0.52 to −0.02) after 18 months, compared with psychoeducation. Very few participants (<10%) started new tic treatment during follow-up. The cost difference in ERP compared with psychoeducation was £304.94 (−139.41 to 749.29). At 18 months, the cost per QALY gained was £16,708 for ERP compared with psychoeducation. **Conclusions:** Remotely delivered online ERP is a clinical and cost-effective intervention with durable benefits extending for up to 18 months. This represents an efficient public mental health approach to increase access to behavioural therapy and improve outcomes for tics. **Keywords:** Tic disorders; randomised controlled trial; long-term follow-up; exposure and response prevention; digital intervention.

Introduction

Tic disorders including Tourette syndrome (TS) and chronic tic disorder (CTD) are classified as neurodevelopmental disorders characterised by motor and/or vocal tics (DSM-5, 2013). Tics are sudden, rapid, nonrhythmic movements or vocalisations that typically begin between the ages of 5 and 7 years, with tic severity usually peaking between the ages of 10 and 13 years and then reducing during late adolescence and early adulthood (Bloch & Leckman, 2009). Tic medications (e.g. clonidine, guanfacine, risperidone and aripiprazole) and habit reversal therapy (HRT)/comprehensive behavioural intervention for tics (CBIT) currently have the most extensive evidence base for the treatment of tic disorders (Pringsheim et al., 2019). However, less is

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known about the efficacy of exposure and response prevention (ERP), a behavioural therapy where patients learn to tolerate the uncomfortable urge (often called the 'premonitory urge') to tic (exposure) while actively controlling their tics (response prevention) (Verdellen, Keijsers, Cath, & Hoogduin, 2004).

As access to behavioural treatments is limited due to an insufficient number of trained therapists relative to demand, online-delivered therapy is an attractive delivery option where only minimal therapist input is required. A small Swedish pilot study which delivered guided self-help behavioural therapy for tics in an online remote format showed ERP to have significant improvement whereas HRT did not in 23 young people. It may be that ERP can be viewed as a 'simpler' intervention than HRT, in that all tics are controlled simultaneously, whereas with HRT, a specific competing response is implemented for each tic (Andrén et al., 2019). For this reason, ERP was selected for the current study, alongside the additional components (social support and functional analyses) which also form part of CBIT (Piacentini et al., 2010).

In the largest randomised controlled trial (RCT) of any behavioural therapy for tic disorders to date (Hall et al., 2019), the online remote behavioural intervention for tics (ORBIT) trial randomised 224 participants aged 9–17 years with tics to receive therapist-supported, parent-assisted, remote ERP therapy or therapist-supported, parent-assisted, remote psychoeducation. Children and adolescents and their supporter (usually a parent) accessed the content via an online system originally developed and piloted in Sweden called 'BIP' [Barninternetprojektet (Child Internet Project); http://www.bup.se/bip] (Andrén et al., 2019). Researchers masked to treatment assignment conducted assessment measures, including the Yale Global Tic Severity Scale Total Tic Severity Score (YGTSS-TTSS) at baseline and at the 3-month (primary endpoint at the end of treatment) and 6-month follow-ups (ORBIT Phase 1). The Phase 1 analysis up to 6-month postrandomisation found evidence of a greater, and clinically meaningful, decrease in tic severity (4.5 points) in the ERP group compared with the psychoeducation group (1.6 points), with more children and adolescents in the ERP group than the psychoeducation group (36% vs. 20%, respectively) classified as treatment responders at the primary endpoint (Hollis et al., 2021). Of those who received ERP, 47% achieved responder status at the 6-month follow-up. A trial process evaluation reported that the intervention was delivered with high fidelity and that participants found the mode of delivery highly acceptable (Khan et al., 2021). Due to the short duration of follow-up in Phase 1, a full health economic analysis was not conducted.

To our knowledge, no health economic evaluations have ever been conducted for any tic disorder treatments, and hence, the societal benefits of such treatments are unclear. Given that guided online behavioural interventions can be delivered with less highly trained therapist support and require less therapist time than traditional face-to-face interventions, it is likely that online delivery of these interventions will not only expand access to evidence-based treatments but also reduce treatment costs for services. Moreover, only one study in the tic disorder treatment literature, either for psychotherapy or medication, has prospectively followed participants beyond 12 months to assess treatment durability (Espil et al., 2021). However, this study examined CBIT, and not ERP, and participants were followed up 11 years after their participation in the RCT and did not include a health economic analysis.

The current study reports the long-term naturalistic follow-up of the ORBIT trial (Phase 2). We aimed at examining whether therapist-supported, parent-assisted, remote ERP was clinically and cost-effective at 12 and 18 months after treatment began compared with therapist-supported, parent-assisted, remote psychoeducation in children and adolescents with tic disorders.

Methods

Trial design

The online remote behavioural intervention for tics (ORBIT) trial design has been described previously (Hall et al., 2019; Hollis et al., 2021). ORBIT was a two-arm, superiority parallel-group, single-blind, multicentre RCT. The trial was conducted across two Child and Adolescent Mental Health Services (CAMHS) in England with participants recruited from these two sites, across 16 participating CAMHS or community paediatric clinics in England, or by self-referral via websites [the study website and Tourettes Action (UK tic disorder charity) website].

The trial consisted of two phases: Phase 1 was an intention-to-treat (ITT), parallel-group follow-up for 6-month postrandomisation (primary endpoint at 3 months), and the findings of this have been previously reported (Hollis et al., 2021). Phase 2 was a naturalistic follow-up to 18-month postrandomisation, whereby participants were permitted to use alternative treatments in accordance with standard practice recommended by their usual treating clinician. Here, we present the Phase 2 findings.

Participants

Full eligibility criteria have been reported previously (Hollis et al., 2021). In brief, eligible participants were aged 9–17 years with a moderate/severe tic disorder (TS or CTD) defined as scores on the YGTSS-TTSS (Leckman et al., 1989) of >15, or >10 if only motor or vocal tics were present. The main exclusion criteria were engaging in a behavioural intervention for tics in the past 12 months, starting or stopping tic medication within the previous 2 months, and suspected moderate/severe intellectual disability.

Participants aged under 16 years were required to have signed parent/guardian consent and provide their own assent. Participants aged 16–17 years signed their own consent and had parent/guardian consent. Ethics approval was received from Northwest Greater Manchester Research Ethics Committee (ref. 18/NW/0079) and prospectively registered with the ISRCTN (ISRCTN70758207) and ClinicalTrials.gov (NCT03483493).

Randomisation

Randomisation was performed on a web-based system by blinded outcome assessors, using a 1:1 ratio and stratified by study site using block randomisation with varying block sizes. For this naturalistic extended follow-up, outcome assessors were aware of the findings of Phase 1 analysis at a group level. However, they did not know individual participant treatment group allocation. Participants were not directly informed of their allocation but may have been able to determine this once treatment commenced.

Procedures

Participants attended a baseline assessment at one of the two study sites, where outcome assessors established eligibility using standardised measures and obtained informed consent (Hall et al., 2019; Hollis et al., 2021). Measures included the YGTSS assessment to determine presence and severity of tics.

Participants received either online, therapist-supported ERP (the intervention group) or online, therapist-supported psychoeducation (the active control group). Both interventions were delivered via the 'BIP' platform. A description of the interventions has been previously published (Hall et al., 2019; Hollis et al., 2021).

Both the ERP and the psychoeducation intervention were designed to be completed over 10 weeks and consisted of 10 web-based chapters for the child/adolescent and 10 different parallel chapters for parent/carers. The therapist supported the interventions through asynchronous contact (usually via online text messages sent through BIP) during the 10 weeks. The therapist role was to promote engagement with the intervention and answer any questions, but they did not deliver any therapeutic content. The therapist aimed to have 10–20 min' contact time with the family each week. Once chapters were completed and therapist support was withdrawn at 12 weeks, participants were free to log into BIP content up to the 12-month follow-up. Qualitative follow-up analysis of the ERP intervention group indicated that very few did so (Khan et al., 2021).

Follow-up measures were collected remotely (via videoconferencing or telephone) and via an online database, embedded in the BIP digital platform. Follow-up measures were completed at midtreatment point (5 weeks), 3 and 6 months (this formed Phase 1). For Phase 2, follow-up measures were at 12- and 18-months postrandomisation.

Outcomes

The key outcome of interest was tic severity as measured by the YGTSS-TTSS; this was the primary outcome measure in Phase 1 (Hollis et al., 2021). The YGTSS is a semistructured interview, with a total score ranging from 0 to 50 (higher scores indicating greater severity). The YGTSS was conducted by a blinded outcome assessor who had undergone mandatory training and 6-monthly agreement checks with an expert rater (Hollis et al., 2021).

Other outcomes completed via interview were the YGTSS impairment score (range 0–50); the Clinical Global Impression – Improvement scale (CGI-I) (Guy, 1976) to measure improvement; the Children's Global Assessment Scale (CGAS; Shaffer et al., 1983) to assess overall functioning; a modified version of the child and adolescent service use schedule (CA-SUS; Byford et al., 2007) to measure healthcare resource use, including specialist tic services.

Measures completed online by the parent/carer included the following: the Parent Tic Questionnaire (PTQ; Chang, Himle, Tucker, Woods, & Piacentini, 2009) as a parent measure of tic presence and severity, which was also completed at 5 weeks (midtreatment); the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1999) to assess general emotional and behavioural concerns; proxy (parent) Child Health Utility 9D (CHU9D; K Stevens, 2010) to assess health-related quality of life (HRQoL).

Measures completed online by the child/young person included the following: the Mood and Feelings Questionnaire (MFQ; Angold, Costello, Messer, & Pickles, 1995) to assess low mood, which was also completed at 5 weeks (midtreatment); the Spence Childhood Anxiety Scale (SCAS; Spence, 1998) to assess anxiety; the CHU9D; and the Child and Adolescent Gilles de la Tourette Syndrome – Quality of Life Scale (C&A-GTS-QoL; Cavanna et al., 2013) to assess disease-specific quality of life. Adverse events were not recorded as part of the long-term follow-up.

Statistical analysis

The trial was originally powered for a primary outcome of the YGTSS-TTSS requiring a sample of 220 participants at the primary endpoint (Phase 1) (Hall et al., 2019; Hollis et al., 2021). For the current study (long-term follow-up), power was not specified.

A predefined statistical analysis plan (SAP) was approved by the Trial Steering Committee. Analysis was conducted using Stata (version 16) and performed on a modified intention-to-treat basis, in which all available data were analysed according to the participants' original allocation group.

Clinical and mental health outcomes at the 12- and 18-month postrandomisation follow-ups were summarised by randomised group using mean [standard deviation (*SD*)] or count (percentage), respectively, for continuous and categorical data. A single linear mixed model was fitted for each continuous outcome, with measures from all available time points (midtreatment, 3, 6, 12 and 18 months) as the repeated measures outcome and a random effect of participant to account for correlations between the repeated measures on each individual at different time points. The main explanatory variables were treatment, time and the treatment-by-time interaction, adjusting for site and the baseline measure of the outcome. Since correlations are commonly smaller over longer time periods, we adjusted for baseline through an interaction with time, which allowed correlations with baseline to differ between follow-up times. The effects of the intervention at 12 and 18 months were estimated from this model.

The statistical model for the CGI-I did not adjust for baseline since this is a measure of change. As is standard in the field, we defined treatment response as scores of 'improved' or 'much improved' on the CGI-I. Response to treatment was compared between study arms using separate logistic regression models at 12 and 18 months, adjusting for site and reported as odds ratios (OR).

Changes in tic medication and behavioural therapy status between 6 and 12 months and between 6 and 18 months are summarised descriptively by study arm and for the sample overall using counts (*N*) and percentages (%). For all models, estimates and 95% confidence intervals are reported.

A full economic evaluation was conducted. additional information can be found in Appendices S1–S6. Unit costs are reported in Appendix S1, Table S1. Healthcare resource use and costs were summarised by randomised group at baseline and 6 and 18 months (Appendices S1–S6). The mean difference in costs and 95% confidence interval for each resource use type was calculated using regression analysis to adjust for baseline costs, site and bias corrected bootstrapping with 1,000 iterations for complete cases (complete resource use at baseline, 3-, 6-, 12- and 18-month follow-up).

Utility calculated from the preference-based algorithm (Stevens, 2011) was used to calculate quality-adjusted life years (QALYs) and is reported by randomised group (mean and *SD*) using results from the proxy-parent (primary QALY measure). Young people also self-completed the CHU9D. Mean

QALYs reported at 6 and 18 months were calculated using the area under the curve method, (Hunter et al., 2015) with mean difference adjusting for baseline CHU9D and site.

Cost-effectiveness is reported using an incremental cost-effectiveness ratio (ICER) for the mean cost per point difference in YGTSS-TTSS and mean cost per QALY between the ERP intervention and psychoeducation control from the health and social care cost perspective at 18 months. Mean incremental YGTSS-TTSS was calculated from YGTSS-TTSS at 18 months, adjusting for baseline and site. For the intervention arm, costs include the cost to the platform, therapist time, supervision and training, as calculated in the Phase 1 results (Hollis et al., 2021). Psychoeducation may be offered more widely by health services and thus available in other formats (i.e. not online), as the control arm acts as a proxy for this, we do not include any platform costs for the control. The ICERs were calculated using seemingly unrelated regression (SUR; Stata command SUREG) to account for the correlation between costs and outcomes. Adjusted, bootstrapped SUR YGTSS-TTSS, QALYs and cost data were used to calculate the probability that the intervention is cost-effective compared with the control for a range of cost-effectiveness threshold values. A cost-effectiveness plane of the bootstrapped results is also reported for both the YGTSS-TTSS analysis and QALY analyses. All costs are reported in 2019/2020 British Pounds. Costs and QALYs after 12 months have been discounted at a rate of 3.5% (NICE, 2013).

Results

In total, 445 potential participants registered interest in the trial, of which 210 were excluded following remote initial screening measures and a further 11 were excluded at the in-person screening and baseline appointment. Thus, 224/445 (50.3%) participants were randomised, 112/224 (50.0%) into the ERP group and 112/224 (50.0%) into the psychoeducation group.

Participant enrolment began on 8 May 2018 and ended on 30 September 2019. The last participant completed the final 18-month follow-up on 12 April 2021; at this point, the ORBIT trial was completed. Participant flow through the trial is shown in Figure 1.

Participants had a mean age of 12 years, were predominately male (177/224; 79%) and of white ethnicity (195/224; 87%). Very few (13%; 30/224) participants were receiving medication for tics (Table 1). Randomisation achieved a good balance in terms of participant characteristics (Table 1) between the two groups. Engagement with the intervention was high for both groups with 88% (99/112) in the ERP group and 94% (105/112) in the psychoeducation group receiving at least the minimum treatment dose (Hollis et al., 2021). With reference to the key outcome of interest, the YGTSS-TTSS, at 12 months, data were collected from 91/112 (81%) in both the ERP group and psychoeducation group, and at 18 months 89/112 (79%) from the ERP group and 90/112 (80%) from the psychoeducation group. The only predictor of missingness was site, which was included as a covariate in the statistical model. However, data from measures that were not directly collected or

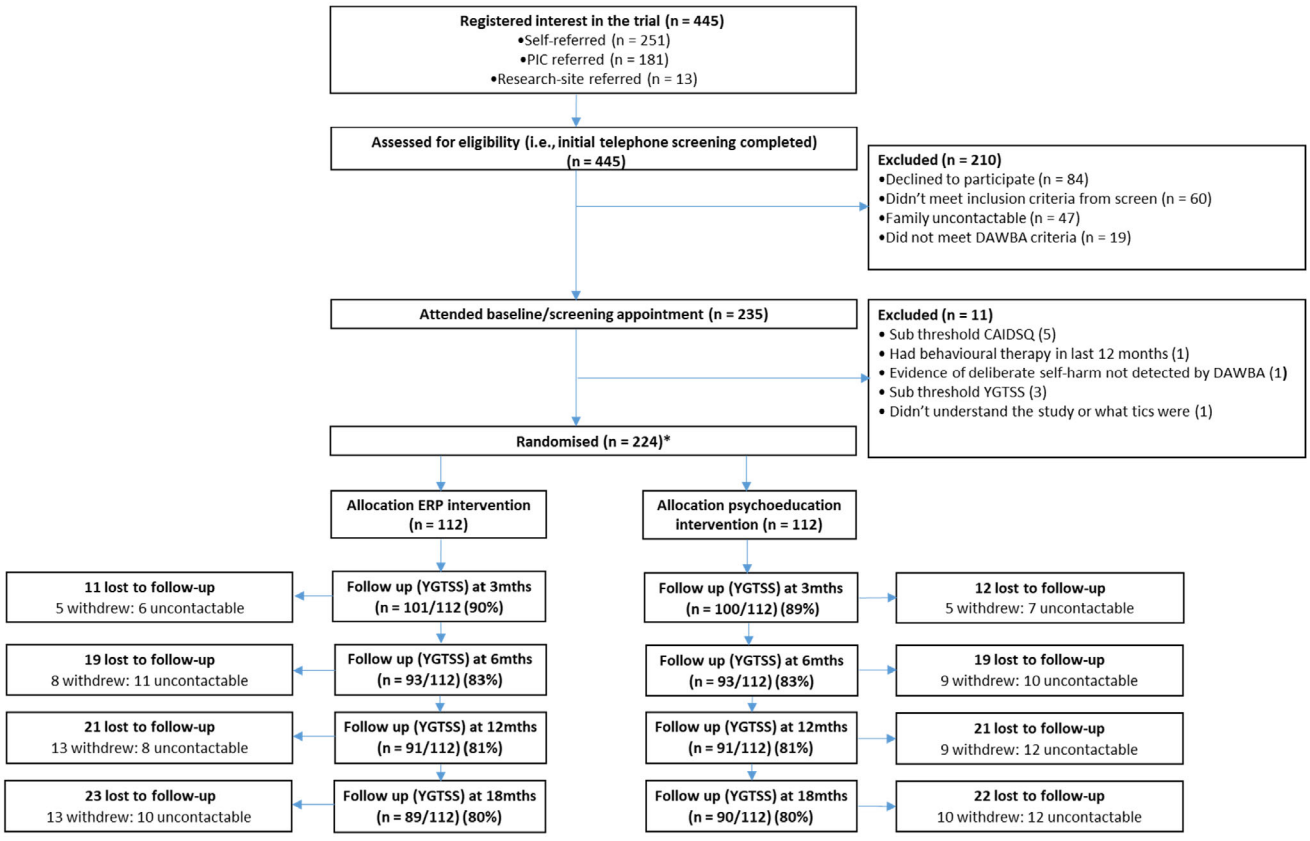

Figure 1 Trial recruitment and retention

Table 1 Demographics at baseline

	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%)
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%)

Statistics are counts (N) and percentages (%) unless otherwise specified. 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. Insufficient information was supplied to assess bipolar disorder for all participants. *SD*, standard deviation.

completed by the outcome assessors (e.g. the PTQ, MFQ, SCAS, SDQ, C&A-GTS-QoL) contained a considerable amount of missing data (Appendix S7; Table S17) and thus should be interpreted with caution. In all cases, the quantity of missing data was similar between randomised groups.

Primary outcome at 12- and 18-month postrandomisation

At study baseline, the mean YGTSS-TTSS in the ERP group was 28.4 (*SD*: 7.7) and in the psychoeducation group it was 28.4 (*SD*: 7.1). At 12 months, the mean YGTSS-TTSS in the ERP group was 21.7 (*SD*: 8.8) compared with 24.9 (*SD*: 7.3) in the psychoeducation group. At 18 months, this was 21.5 (*SD*: 9.0) in the ERP group versus 23.9 (*SD*: 8.4) in the psychoeducation group. After adjustment for tic severity at baseline and site, the analysis revealed that the ERP intervention reduced YGTSS-TTSS by 2.64 points (95% CI: −4.48 to −0.79) with an effect size of −0.36 (95% CI: −0.61 to −0.11) after 12-month follow-up and by 2.01 points (95% CI: −3.86 to −0.15) with an effect size of −0.27 (95% CI -0.52 to −0.02) after 18-month follow-up, compared with the psychoeducation group (Table 2). A forest plot of standardised effect sizes for the clinical outcomes is presented in Figure 2.

Secondary outcomes at 12- and 18-month postrandomisation

With reference to other measures of tics (Table 2; Figure 2), the parent-reported PTQ demonstrated lower tic severity in the ERP group compared with the psychoeducation group at 12 months (−9.89; 95% CI: −16.01 to −3.77), but no evidence of a difference at 18 months. There was no evidence of an intervention effect at either time point on the YGTSS impairment score.

Other outcomes, including young person-reported low mood (MFQ) and anxiety (SCAS), showed a greater reduction in symptoms in the ERP group compared with the psychoeducation group at both 12 months (MFQ = −2.93; 95% CI: −5.77 to −0.09: SCAS = −6.11; 95% CI: −10.41 to −1.81) and 18 months (MFQ = −4.87; 95% CI: −8.00 to −1.75: SCAS = −9.41; 95% CI: −14.11 to −4.70). There was evidence of greater improvement in the ERP group for young person-reported tic-specific quality of life (C&A-GTS-QoL) at both time points (12 months = −5.79; 95% CI: −10.28 to −1.30: 18 months = −9.00; 95% CI: −13.98 to −4.01). There was also some evidence of greater improvement in the ERP group for the outcome assessor-reported measures of overall functioning (CGAS) and global improvement (CGI-I) at both 12 (CGAS = 2.85; 95% CI: 0.15 to 5.56: CGI-I = −0.43; 95% CI: −0.75 to −0.10) and 18 months (CGAS = 3.18; 95% CI: 0.47 to 5.90: CGI-I = −0.38; 95% CI: −0.71 to −0.05). However, there was no difference in parent-reported general emotional and behavioural functioning (SDQ) at either time point (Table 2).

As Phase 2 was a naturalistic follow-up, participants were allowed to start new behavioural or pharmacological treatments for tics during this time. However, very few participants started a new treatment after 6 months (end of Phase 1), with only 11 (6%) starting a new medication and 6 (3%) starting a new tic therapy from 6 to 12 months, and only 7 (4%) starting a new medication and 2 (1%) starting a new tic therapy from 6- to 18-month time point (see Appendix S7; Table S18). The majority of

Table 2 Effect of the exposure and response prevention (ERP) intervention at 12- and 18-month follow-up

	12-month follow-up			18-month follow-up		
	Psychoeducation ($N = 112$), mean (*SD*)	ERP ($N = 112$), mean (*SD*)	Estimated difference (95% CI)	Psychoeducation ($N = 112$), mean (*SD*)	ERP ($N = 112$), mean (*SD*)	Estimated difference (95% CI)
Outcomes						
Total Tic Severity Score (TTSS) on the Yale Global Tic Severity Scale (YGTSS)	24.9 (7.3)	21.7 (8.8)	−2.64 (−4.48 to −0.79)	23.9 (8.4)	21.5 (9.0)	−2.01 (−3.86 to −0.15)
Impairment score on the Yale Global Tic Severity Scale (YGTSS)	17.5 (11.1)	14.8 (11.6)	−2.41 (−5.35 to 0.53)	16.9 (12.1)	15.8 (11.5)	−0.97 (−3.93 to 1.99)
Parent Tic Questionnaire (PTQ)	43.0 (25.3)	30.7 (23.8)	−9.89 (−16.01 to −3.77)	35.9 (25.6)	28.1 (19.1)	−2.15 (−8.83 to 4.53)
Clinical Global Impression – Improvement (CGI-I)	3.07 (0.9)	2.67 (1.09)	−0.43 (−0.75 to −0.10)	2.86 (1.1)	2.49 (1.36)	−0.38 (−0.71 to −0.05)
Children's Global Assessment Scale (CGAS)	75.0 (12.9)	77.4 (13.3)	2.85 (0.15 to 5.56)	77.3 (12.6)	79.3 (13.5)	3.18 (0.47 to 5.90)
Strengths and Difficulties Questionnaire (SDQ)	14.6 (6.4)	14.4 (5.6)	−0.86 (−2.31 to 0.58)	13.8 (5.4)	13.6 (6.1)	−0.71 (−2.26 to 0.84)
Mood and Feelings Questionnaire (MFQ)	14.3 (11.6)	11.4 (10.4)	−2.93 (−5.77 to −0.09)	16.0 (14.6)	10.9 (10.0)	−4.87 (−8.00 to −1.75)
Spence Child Anxiety Scale (SCAS)	29.9 (19.1)	25.3 (17.1)	−6.11 (−10.41 to −1.81)	32.6 (20.4)	24.3 (18.6)	−9.41 (−14.11 to −4.70)
Child and Adolescent Gilles de la Tourette Syndrome–Quality of Life Scale (C&A-GTS-QOL)	32.2 (16.8)	25.5 (16.8)	−5.79 (−10.28 to −1.30)	36.8 (21.1)	26.0 (16.6)	−9.00 (−13.98 to −4.01)

Statistics are mean (*SD*) unless otherwise specified. Statistical models adjusted for the baseline measure of the outcome in question (with the exception of the CGI-I) and site using a single linear mixed model for each outcome, with measures from all available time points as a repeated measures outcome and a random effect of participant to account for correlations between repeated measures within individuals. Higher scores on the C&A-GTS-QOL indicate *worse* quality of life. The quantity of missing data for all outcomes was similar in both trial arms. At 12-month follow-up, there were 21 missing observations (19%) for YGTSS-TTSS in the ERP therapy arm compared to 21 (19%) in the psychoeducation arm. At 18-month follow-up, there were 22 missing observations (20%) for YGTSS-TTSS in the ERP therapy arm compared to 23 (21%) in the psychoeducation arm. CI, confidence interval; *SD*, standard deviation.

participants were not using tic medication or accessing tic therapy at 12 months (no tic medication = 90%; no tic therapy = 94%) or 18 months (no tic medication = 92%; no tic therapy = 96%). As the number of participants who stopped, started or changed tic medication or therapy after 6 months was considered too small to provide meaningful results, we did not conduct the sensitivity analysis on the YGTSS-TTSS for therapeutic changes as outlined in our SAP.

In line with the Phase 1 report (Hollis et al., 2021), we repeated an unplanned post hoc analysis comparing positive treatment response as defined by a rating of 1 or 2 (very much/much improved) on the CGI-I. The findings showed a greater treatment response with ERP at 12 months with 46% classed as responders compared with 27% classed as responders to psychoeducation (OR 2.27; 95% CI: 1.23 to 4.22). Similar effects were seen at 18 months with 55% classed as responders to ERP versus 41% to psychoeducation (OR 1.80; 95% CI: 0.99 to 3.27). Table 3 shows that participants who responded at 6 months were more likely to continue to respond at later follow-up and less likely to relapse if they were in the ERP group.

Health economic analysis results

At 18 months, there was no significant difference in health and social care costs between the two groups (see Appendices S3 and S4). When the cost of the ERP intervention is added, the mean adjusted, discounted difference in total 18-month costs of the intervention compared with the psychoeducation control is £304.94 (−139.41 to 749.29). Assuming a change in YGTSS-TTSS of −1.68 (−3.74 to 0.39) at 18 months, the mean incremental cost per point reduction in YGTSS-TTSS is £182 (see Figure 3).

Preference-based HRQoL and QALYs are reported in Appendix S4. At 18 months, the incremental cost per QALY gained, using proxy (parent) completed CHU9D, was £16,708 for the intervention compared with the control. Bootstrapped iterations are shown on the cost-effectiveness plane in Appendix S4. Further secondary and sensitivity analyses are reported in Appendix S4.

Discussion

The benefits of internet-delivered, therapist-supported and parent-assisted ERP for tics in

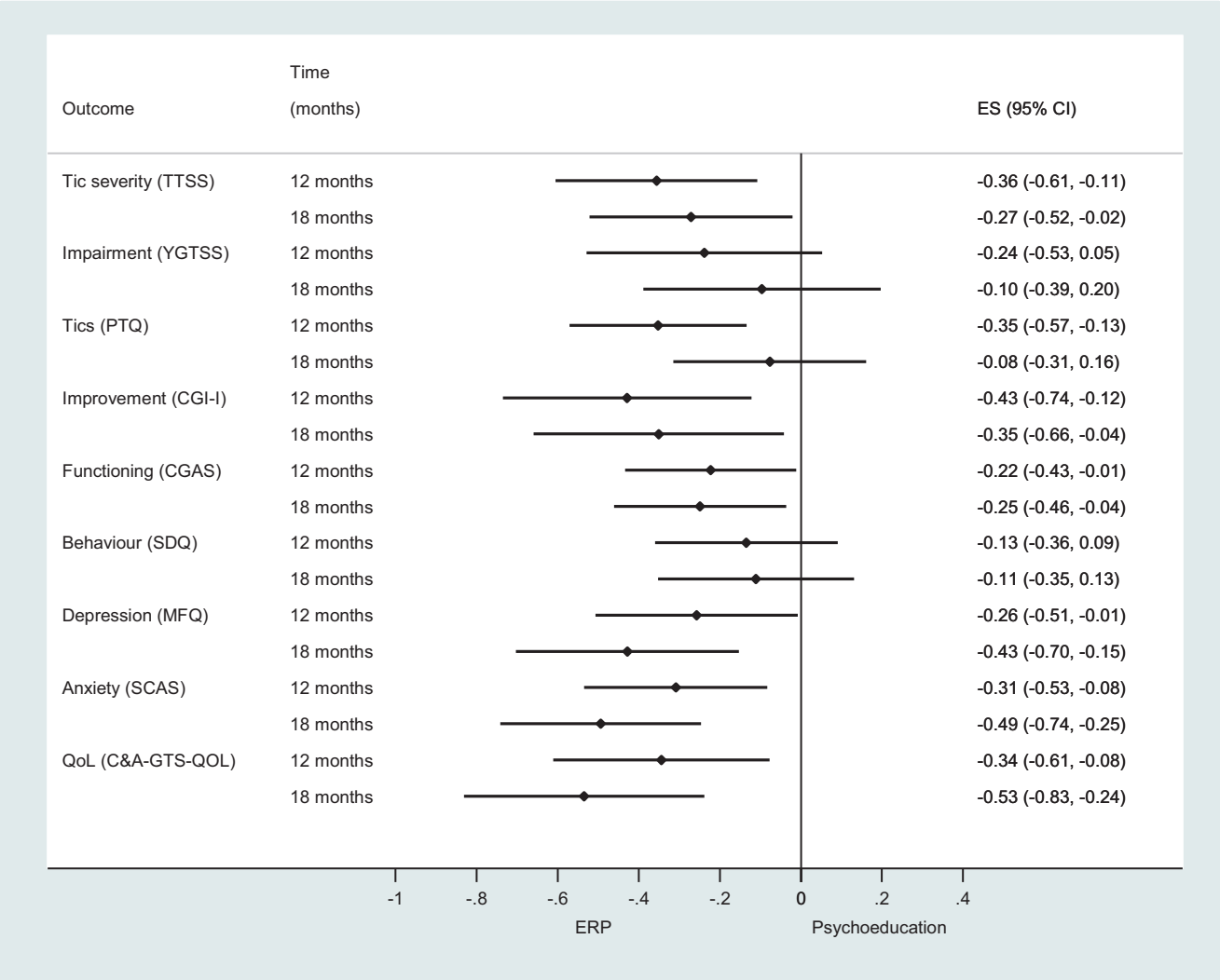

Figure 2 Primary and secondary outcomes at 12- and 18-month follow-up. Forest plot of standardised effect sizes

Table 3 Response to treatment at 12- and 18-month follow-up

	12-month follow-up			18-month follow-up		
	Psychoeducation ($N = 91$), N (%)	ERP ($N = 91$), N (%)	Odds ratio (95% CI)	Psychoeducation ($N = 90$), N (%)	ERP ($N = 89$), N (%)	Odds ratio (95% CI)
CGI-I scored indicating much or very much improved from baseline (responded to treatment)	25 (27%)	42 (46%)	2.27 (1.23 to 4.22)	37 (41%)	49 (55%)	1.80 (0.99 to 3.27)
Responders at 6 months						
Continued response at later follow-up	13/26 (50%)	26/40 (65%)	–	14/26 (54%)	30/39 (77%)	–
Relapsed responder at later follow-up	13/26 (50%)	14/40 (35%)		12/26 (46%)	9/39 (23%)	
Nonresponders at 6 months						
Continued nonresponse at later follow-up	51/62 (82%)	33/46 (72%)	–	38/60 (63%)	29/45 (64%)	–
New responder at later follow-up	11/62 (18%)	13/46 (28%)		22/60 (37%)	16/45 (36%)	

Statistics are counts (N) and percentages (%) unless otherwise specified. Statistical models adjusted for site. CGI-I, Clinical Global Impression – Improvement scale; CI, confidence interval.

children and adolescents are sustained long term for up to 18 months after the start of treatment. The effect size of online ERP compared with psychoeducation was larger at 12 months (−0.36) than at the end of treatment 3-month primary endpoint (−0.31). At 12 months, 46% were classed

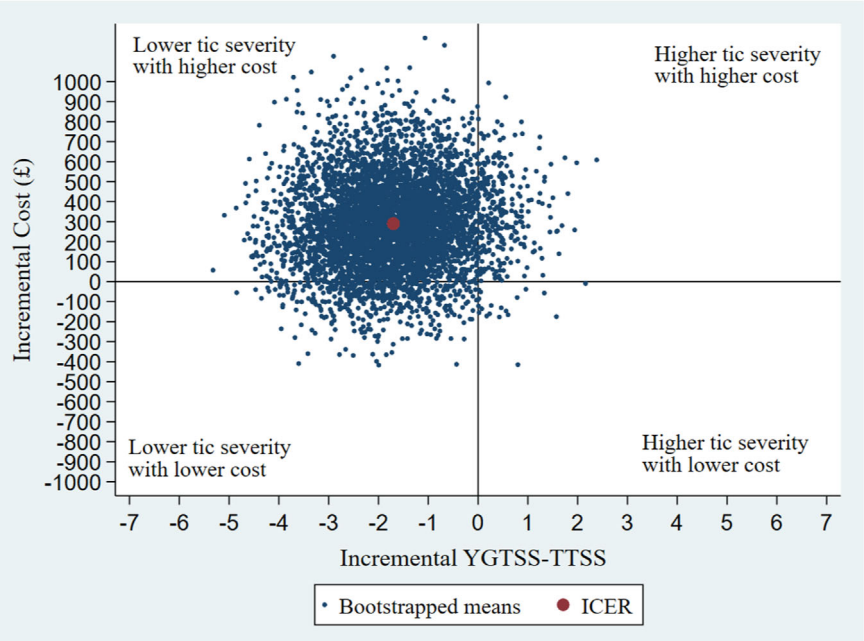

Figure 3 ICER and CEP for cost per point reduction in YGTSS-TTSS. As a reduction in TTSS is an improvement, the interpretation is reversed compared with a usual CEP looking at incremental QALYs. The ICER for the TTSS analysis sits in the Northwest quadrant, in this case suggesting the intervention has a greater positive impact compared with the control, at a greater cost. The decision on whether the intervention is cost-effective therefore depends on the decision-maker's cost-effectiveness threshold. CEP, cost-effective plane; ICER, incremental cost-effectiveness ratio; TTSS, total tic severity score; YGTSS, Yale Global Tic Severity Scale

as responders to online ERP with this increasing to 55% at 18 months. This extends and strengthens our previous findings, which showed that online ERP was effective at 3 months after the start of treatment and durable for up to 6 months. In addition, extended follow-up showed those receiving online ERP compared with online psychoeducation had reduced scores for low mood and anxiety at 12 and 18 months and superior tic-specific quality of life, with the largest effects seen at 18 months. However, there were no group differences for YGTSS impairment and large amount of missing data for the secondary self-report measures of mood, anxiety and tic-specific quality of life indicates that these findings should be interpreted with caution.

This study was planned as a naturalistic follow-up beyond 6 months, with participants free to access tic medication and therapy as clinically required. However, very few participants (less than 10%) started new treatments in either arm during the extended follow-up period although at least half were classed as nonresponders. Hence, this study essentially represents an intention-to-treat, parallel-group, long-term 18-month follow-up of online ERP for tics in children and young people. Retention to the primary outcome measure (YGTSS Tic Severity) was high at 12 months (81% in both arms) and 18 months (>79% in both arms).

The low proportion of participants starting new treatments suggests that the sustained benefit seen in the ERP arm is unlikely to be due to greater access to new tic treatments during the follow-up period. This finding also highlights the lack of availability of behavioural treatment for tics in the United Kingdom outside this trial with so few receiving treatment during the extended follow-up although many needed it. Another possibility, which could apply to both arms of the study, is that the interventions were sufficient in meeting the needs of the participants and hence no further intervention was required. However, we think it unlikely that the intervention was sufficient for all given that around half of participants were classified as nonresponders. In addition, the finding of moderate mean tic severity during the follow-up with a large standard deviation suggests that while many participants showed major benefits from the intervention, others did not. Hence, further implementation research will 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 nonresponders or partial responders being 'stepped-up' to more intensive face-to-face therapy.

Long-term follow-up studies of any treatments for chronic tics have been exceedingly rare. This is the first controlled study to demonstrate the long-term effectiveness (beyond 6 months) of ERP for tics and the first to show that online ERP is cost-effective compared with an active control. Given the follow-up period for some participants overlapped with the COVID-19 pandemic period, we have previously explored the potential impact of this. Our findings revealed no significant differences in tic symptoms between participants who were assessed before or during the pandemic. The result was not influenced

by age or gender or by symptoms of anxiety or ASD. From this, we concluded that COVID-19 did not significantly impact tics in our sample of children and young people who already had an existing tic disorder (Hall et al., 2022).

The magnitude of effect of this online ERP intervention, which was maintained for up to 18 months, is modest and about half the size reported from previous superiority trials of face-to-face HRT/CBIT for tics which have followed participants for 6 to 9 months (Piacentini et al., 2010). 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 of online behavioural therapy for tics is not to replace face-to-face therapy, but to allow this scarce 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.

The health economic analysis showed that the ICER for the cost per QALY analysis falls below the NICE cost-effectiveness threshold commonly used in health technology assessments of £20,000 per QALY; there is a 65% probability that the intervention is cost-effective at this threshold. The costs and benefits of online ERP to children and young people with tic disorders are likely to extend beyond these 18-month trial data, and hence, further work is required to project the findings over a longer time horizon using decision modelling. This would also make it possible to include other comparators, such as face-to-face therapy, to evaluate any cost savings of relatively cheap, but effective online behavioural interventions compared with 'gold standard' best practice.

The study has some limitations. First, as it is the first long-term study of the effectiveness of therapist-supported, online ERP, replications are required. In addition, future clinical and cost-effectiveness comparisons of digital online versus face-to-face ERP or CBIT will be needed. Second, as very few participants received other tic treatments either before the trial or during the naturalistic follow-up, we were unable to evaluate the potential moderating effects of other treatments, such as tic medication. However, this represents the reality of clinical services for children and young people with tics in the United Kingdom and is very unlikely to differ from other western/developed countries. This paucity of tic treatment in standard care, while a significant concern for patients, is a design strength when evaluating long-term trial intervention effects uncontaminated by other treatments. Third, the participants were predominantly white Caucasian, which limits generalisability to populations with a substantially different ethnic mix. Fourth, our secondary self-reported outcomes are subject to potential recall bias, which means these findings should be interpreted with caution. Fifth, although prior analyses have shown that anxiety disorder and ADHD comorbidities do not moderate short-term treatment effects of online ERP for tics, we cannot exclude possible effect modification during longer-term follow-up.

In summary, evidence from this trial suggests that online therapist-supported ERP is an effective behavioural therapy for reducing tic symptoms, which has durable and sustained long-term benefits. In healthcare settings where tic treatments are difficult to access, therapist-supported online ERP as a first-line intervention could greatly increase the availability of a durable and cost-effective behavioural treatment for children and adolescents with tic disorders.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1. Aim.
A**ppendix S2.** Outputs.
Appendix S3. Methods.
Appendix S4. Results.
Appendix S5. Discussion.
Appendix S6. References.
Appendix S7. Supplementary analysis.
Table S1. Unit costs for specialist tic services.
Table S2. Unit costs for contacts with professionals in the community.
Table S3. Unit costs for hospital stays and emergency services.
Table S4. Unit costs for wider societal costs.
Table S5. Intervention costs summary.
Table S6. Data completeness for the CA-SUS.
Table S7. Use of specialist tic services (not including any services specific to the Online ERP intervention or psychoeducation).
Table S8. Other service use.
Table S9. Medication use.
Table S10. Total healthcare cost.
Table S11. Education Support and voluntary services.
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Table S13. Wider costs.
Table S14. Preference based utilities and QALYs using parent completed CHU9D.
Table S15. Preference based utilities and QALYs using child completed CHU9D.
Table S16. Summary of ICERs by outcome and cost perspective.
Table S17. Missing data at 12 and 18 months follow up.
Table S18. Changes in medication and therapy for tics at 12 and 18 months.

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Ethical considerations

Written informed consent was obtained after the procedures had been fully explained; for children under 16 years old, written consent was obtained from the parent/legal guardian and verbal or written assent was obtained from the child/young person.

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Key points

- Previous research has highlighted the difficulty accessing evidence-based behavioural treatments for tics.
- This is the first controlled long-term study on the clinical and cost-effectiveness of online exposure and response prevention (ERP) in children and adolescents with tics.
- Our results strengthen the evidence that online ERP has durable beneficial effects sustained over time.
- At both the 12- and 18-month follow-up time points, participants treated with online therapist and parent-supported ERP showed greater reduction in tic severity compared with participants receiving online psychoeducation.
- Cost-effectiveness analysis showed that the intervention is likely to be considered cost-effective according to NICE thresholds.
- Digitally enabled ERP for tics is an efficient public mental health approach to increase the reach of an effective and durable treatment for children and adolescents with tic disorders.

References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. Arlington, VA: Author.

Andrén, P., Aspvall, K., de la Cruz, L.F., Wiktor, P., Romano, S., Andersson, E., … & Mataix-Cols, D. (2019). 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*, *9*, e024685.

Angold, A., Costello, E.J., Messer, S.C., & Pickles, A. (1995). Development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. *International Journal of Methods in Psychiatric Research*, *5*, 237–249.

Bloch, M.H., & Leckman, J.F. (2009). Clinical course of Tourette syndrome. *Journal of Psychosomatic Research*, *67*, 497–501.

Byford, S., Barrett, B., Roberts, C., Wilkinson, P., Dubicka, B., Kelvin, R., … & Goodyer, I. (2007). Cost-effectiveness of selective serotonin reuptake inhibitors and routine specialist care with and without cognitive–behavioural therapy in adolescents with major depression. *British Journal of Psychiatry*, *191*, 521–527.

Cavanna, A.E., Luoni, C., Selvini, C., Blangiardo, R., Eddy, C.M., Silvestri, P.R., … & Rizzo, R. (2013). Disease-specific quality of life in young patients with Tourette syndrome. *Pediatric Neurology*, *48*, 111–114.

Chang, S., Himle, M.B., Tucker, B.T., Woods, D.W., & Piacentini, J. (2009). Initial psychometric properties of a brief parent-report instrument for assessing tic severity in children with chronic tic disorders. *Child and Family Behaviour Therapy*, *31*, 181–191.

Espil, F.M., Woods, D.W., Specht, M.W., Bennett, S.M., Walkup, J.T., Ricketts, E.J.E.J., … & Peterson, A.L. (2021). Long-term outcomes of behavior therapy for youth with Tourette disorder. *Journal of the American Academy of Child & Adolescent Psychiatry.*, *61*, 764–771.

Goodman, R. (1999). 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*, *40*, 791–799.

Guy, W. (1976). *ECDEU assessment manual for psychopharmacology* (pp. 534–537). Rockville, MD: US Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs.

Hall, C.L., Davies, E.B., Andrén, P., Murphy, T., Bennett, S., Brown, B., … & Hollis, C. (2019). 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*, *9*, e027583.

Hall, C.L., Marston, L., Khan, K., Brown, B.J., Sanderson, C., Andrén, P., … & Hollis, C. (2022). The COVID-19 pandemic and its impact on tic symptoms in children and young people: A prospective cohort study. *Child Psychiatry & Human Development*. doi: 10.1007/s10578-022-01348-1

Hollis, C., Hall, C.L., Jones, R., Marston, L., Le Novere, M., Hunter, R., … & Murray, E. (2021). Therapist-supported online remote behavioural intervention for tics in children and adolescents in England (ORBIT): A multicentre, parallel group, single-blind, randomised controlled trial. *The Lancet Psychiatry*, *8*, 871–882.

Hunter, R.M., Baio, G., Butt, T., Morris, S., Round, J., & Freemantle, N. (2015). An educational review of the statistical issues in analysing utility data for cost-utility analysis. *PharmacoEconomics*, *33*, 355–366.

Khan, K., Hollis, C., Hall, C.L., Murray, E., Davies, E.B., Andrén, P., … & Glazebrook, C. (2021). Fidelity of delivery and contextual factors influencing children's level of engagement: Process evaluation of the online remote behavioral intervention for tics trial. *Journal of Medical Internet Research*, *23*, e25470.

Leckman, J.F., Riddle, M.A., Hardin, M.T., Ort, S.I., Swartz, K.L., Stevenson, J., & Cohen, D.J. (1989). 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*, *28*, 566–573.

NICE, U. (2013). *Guide to the methods of technology appraisal*. London: National Institute for Health and Clinical Excellence (NICE).

Piacentini, J., Woods, D.W., Scahill, L., Wilhelm, S., Peterson, A.L., Chang, S., … & Walkup, J.T. (2010). Behavior therapy for children with Tourette disorder: A randomized controlled trial. *JAMA*, *303*, 1929–1937.

Pringsheim, T., Okun, M.S., Müller-Vahl, K., Martino, D., Jankovic, J., Cavanna, A.E., … & Piacentini, J. (2019). Practice guideline recommendations summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders. *Neurology*, *92*, 896–906.

Shaffer, D., Gould, M.S., Brasic, J., Ambrosini, P., Fisher, P., Bird, H., & Aluwahlia, S. (1983). A children's global assessment scale (CGAS). *Archives of General Psychiatry*, *40*, 1228–1231.

Spence, S.H. (1998). A measure of anxiety symptoms among children. *Behaviour Research and Therapy*, *36*, 545–566.

Stevens, K. (2010). The child health utility 9D (CHU9D). A new, paediatric, preference-based measure of health related quality of life. *PRO Newsletter*, *43*, 11–12.

Stevens, K. (2011). Assessing the performance of a new generic measure of health-related quality of life for children and refining it for use in health state valuation. *Applied Health Economics and Health Policy*, *9*, 157–169.

Verdellen, C.W., Keijsers, G.P., Cath, D.C., & Hoogduin, C.A. (2004). Exposure with response prevention versus habit reversal in Tourettes's syndrome: A controlled study. *Behaviour Research and Therapy*, *42*, 501–511.

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