ORBIT TRIAL PROTOCOL

Long title of the trial	Therapist-guided, parent-assisted remote digital behavioural intervention for tics in children and adolescents with Tourette syndrome: an internal pilot study and single-blind randomised controlled trial
Short title of trial	Online Remote Behavioural Intervention for Tics (ORBIT)
Version and date of protocol	Version 3.0, 16-APR-2018
Sponsor	Nottinghamshire Healthcare NHS Foundation Trust
Sponsor protocol number	Hollis201117
Funder (s)	NIHR Health Technology Assessment (HTA)
Trial registration number	ISRCTN70758207 and NCT03483493
Sites	Multi-site: Great Ormond Street Hospital for Children NHS Foundation Trust and Nottinghamshire Healthcare NHS Foundation Trust
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Sponsor Representative:	Shirley Mitchell: Shirley.mitchell@nottshc.nhs.uk Nottinghamshire Healthcare NHS Foundation Trust, Duncan Macmillan House, Porchester Road, Mapperely, Nottingham, NG3 6AA

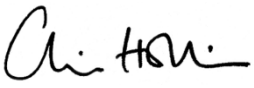
SIGNATURES

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles of GCP, the Sponsor's SOPs, Priment SOPs and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

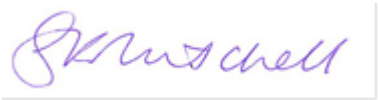
I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator: Professor Chris Hollis

Sign: 

Date: 17-APR-2018

Sponsor Representative: Shirley Mitchell

Sign: 

Date: 17-APR-2018

Priment Representative: Anne Marie Downey

Sign: 

Date: 17-APR-2018

VERSION HISTORY

Version number	Version date	Reason for Change
1.0	20 Dec 2017	First Version
2.0	28 Feb 2018	The 10-week therapist supported intervention may be delivered over 12-weeks. The Trial registration details were added.

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS

Term	Definition
ADHD	Attention deficit hyperactivity disorder
AE	Adverse Event
AR	Adverse Reaction
BIP	Barninternetprojektet (swedish platform)
BT	Behavioural Therapy
C2C	Consent to Contact
C&A-GTS-QoL	Children & Adolescent Gilles de la Tourette Syndrome Quality of Life Scale
CA-SUS	Child and Adolescent Service Use Schedule
CBIT	Comprehensive Behavioural Intervention for Tics
CGAS	Children's Global Assessment Scale
CGI-I	Clinical Global Impressions- Improvement scale
CHU9D	Child Health Utility 9D
CI	Chief Investigator
CRF	Case Report Form
CSRI	Client Service Receipt Inventory
Non-CTIMP	Clinical Trial without an Investigational Medicinal Product
DAWBA	Development and Wellbeing Assessment
DSMB	Data Safety and Monitoring Board
ERP	Exposure and Response Prevention
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
GOSH	Great Ormond Street Hospital
HCPs	Health Care Professionals
HRT	Habit Reversal Therapy
Icbit	Internet-based Cognitive Behavioural Therapy
ICF	Informed Consent Form
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
Main REC	Main Research Ethics Committee
MFQ	Moods and Feelings Questionnaire
NMB	Net Monetary Benefit
NHS R&D	National Health Service Research & Development
NHFCT	Nottinghamshire Healthcare NHS Foundation Trust

OCD	Obsessive compulsive disorder
PI	Principal Investigator
PIC	Patient Identification Centre
PIS	Participant Information Sheet
PMG	Project Management Group
PPI	Patient and Public Involvement
PTQ	Parent Tic Questionnaire
PUTS	Premonitory Urges for Tics Scale
QA	Quality Assurance
QC	Quality Control
QALY	Quality-Adjusted Life-Year
RCT	Randomised Control Trial
REC	Research Ethics Committee
RT	Research Team
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SCAS	Spence Child Anxiety Scale
SCQ	Social Communications Questionnaire
SDQ	Strengths and Difficulties Questionnaire
SDV	Source Document Verification
SNAP-IV	Swanson, Nolan and Pelham fourth edition
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAU	Treatment as Usual
TS	Tourette syndrome
TSC	Trial Steering Committee
YGTSS	Yale Global Tic Severity Scale

3 TRIAL PERSONNEL

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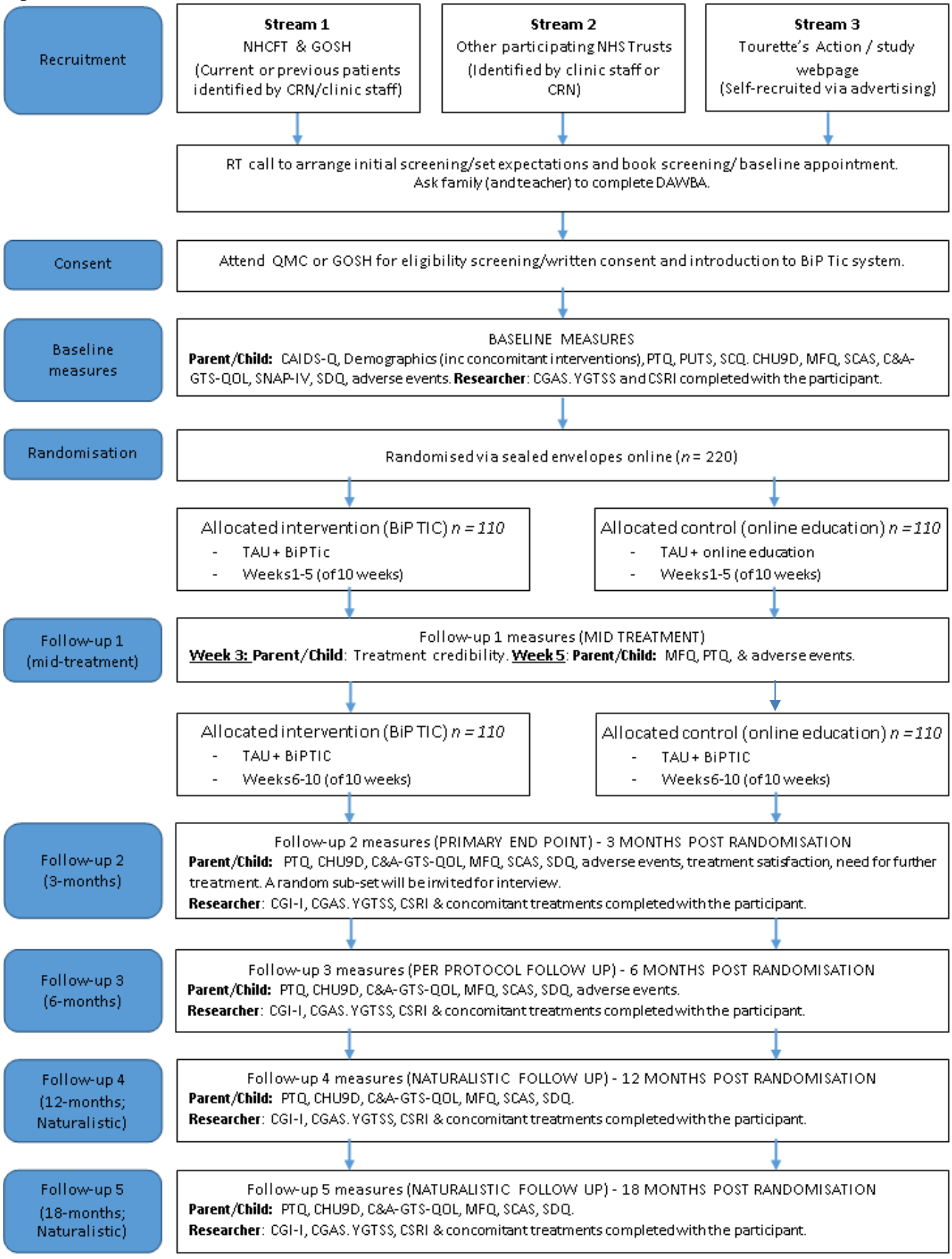
4 SUMMARY

Title:	Therapist-guided, parent-assisted remote digital behavioural intervention for tics in children and adolescents with Tourette syndrome: an internal pilot study and single-blind randomised controlled trial.
Short title:	Online Remote Behavioural Intervention for Tics (ORBIT).
Objectives:	Primary objective: to evaluate the clinical effectiveness of BiP Tic, a therapist-guided, parent-assisted, internet-based behavioural therapy intervention for tics in young people, compared with usual care plus online education. Secondary objectives include 1) optimising the design of the intervention, 2) undertaking an internal pilot, 3) evaluating cost effectiveness and 4) longer term impact, and 5) identifying barriers to implementation.
Type of trial:	Single-blind parallel-group randomised controlled superiority trial, with an internal pilot.
Trial design and methods:	All potential participants attend a screening/baseline appointment at one of the two study centres. Participants who are eligible and have consented will be randomised into one of two study arms. In the experimental arm participants receive 10-weeks of the remotely delivered, therapist guided behaviour therapy. In the control arm participants receive 10-weeks of remotely delivered, therapist guided psychoeducation about tics. Participants will complete outcome measures at baseline, mid treatment, 3, 6, 12 and 18 months post-randomisation. The primary outcome (at 3 months) is the total tic severity score (TTSS) on the Yale Global Scale (YGTSS). Secondary outcomes include measures of: tics (PTQ), general difficulties (SDQ), mood and anxiety (MFQ and SCAS), adverse events, need for further treatment, treatment credibility and satisfaction. Quality of life (CHU9D; C&A-GTS-QOL) and resource use (modified CSRI) will also be collected for the economic evaluation (including a measure of school

	attendance). Researcher completed measures of global functioning (CGAS, CGI-improvement) will also be recorded. Follow-up measures will be completed online or via the telephone/ Webex video-conferencing (YGTSS). The trial will be evaluated 9-months into recruitment by the Project Management Group (PMG), Trial Steering Committee (TSC) and Data and Safety Monitoring Board (DSMB) to check the trial meets the specified stop/go criteria before proceeding. A sub-sample of parents, young people, clinicians and therapists will be interviewed after the collection of the primary outcome at 3-months to explore barriers/facilitators to implementation and refine the intervention for future use.
Participant time in trial:	18-months.
Total trial duration:	36-months (from first participant enrolled to last participant follow-up).
Planned trial sites:	The intervention will be delivered across 2 sites. Multiple Patient Identification Centres (PIC) will be used to identify potential participants (including NHS and non-NHS sites).
Sample:	220 participants
Brief eligibility criteria:	Eligible participants will be aged 9-17 years, with tics assessed on the YGTSS. Exclusion criteria include receiving a therapy for tics in the past 12-months, recent changes to tic medication and intellectual disability/substance use/anorexia nervosa/psychosis/suicidality. See section 10.1 for full details.
Statistical methodology and analysis:	Data will be analysed using the intention to treat principle using complete cases. The primary outcome will be analysed using linear regression controlling for centre (the stratification variable). Secondary outcomes will be analysed using analogous methods to the primary outcome.

5 TRIAL FLOW CHART

Figure 1 below shows the trial flow.



Key: RT = Research team; PUTS = Premonitory Urges for Tics Scale; PTQ = Parent Tic Questionnaire; SCQ = Social Communication Questionnaire; YGTSS = Yale Global Tic Severity Scale; C&A-GTS-QOL = Quality of life scale for patients aged 6-12 years; ; CGAS = Children's Global Assessment Scale; CGI-I = Clinical Global Impressions- Improvement scale; SDQ = Strengths and Difficulties Questionnaire; DAWBA = Development and Wellbeing Assessment; CHU9D = Child Health Utility 9D; CSRI = Client Service Receipt Inventory; MFQ = Moods and Feelings Questionnaire; SCAS = Spence Child Anxiety Scale; TAU = treatment as usual.
Note: The CSRI includes a measure of school attendance. The YGTSS includes both a measure of severity and impairment.

6 INTRODUCTION

6.1 BACKGROUND

Tourette syndrome (TS) is a common, disabling, childhood-onset condition affecting up to 1% of young people (approximately 70,000 people age 7-17 years in England) and associated with high levels of comorbidity, significant distress, psychosocial impairment and reduced quality of life (Hollis et al., 2016). The majority of patients additionally experience comorbidities such as attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), depression, anxiety, and self-injurious behaviour (Freeman et al., 2000), making interventions complex. Evidence-based interventions for the treatment of tics in children and adolescents with TS include both pharmacological treatment and behaviour therapy (BT) (Hollis et al., 2016, Verdellen et al., 2011a, Whittington et al., 2016, Roessner et al., 2011). Two different types of behaviour therapy, Habit Reversal Training (HRT) and Exposure and Response Prevention (ERP), are both effective behavioural therapy (BT) treatments for tics (Verdellen et al., 2011a, Whittington et al., 2016) and the comprehensive behavioural intervention for tics (CBIT) package based on HRT shows similar efficacy to medication (Whittington et al., 2016). While there is no NICE guidance for the management of tics in children and young people with TS, existing European guidelines (Verdellen et al., 2011a) and our recent HTA Evidence Synthesis (Hollis et al., 2016) recommend that BT should be offered first-line for tics in children and adolescents in a stepped-care approach. Despite these recommendations, only 1 in 5 young people with TS are currently able to access BT for tics, while around 50% receive medication (Cuenca et al., 2015), which is associated with a significant risk of adverse effects including weight gain and sedation (Whittington et al., 2016, Roessner et al., 2011). Furthermore, those young people who manage to access BT typically receive four or fewer face-to-face therapy sessions, less than half the number recommended.

The majority of young people surveyed with TS in the UK request greater access to behavioural interventions (Cuenca et al., 2015). However, in the UK there is a desperate lack of expert therapists trained to deliver behavioural interventions for tics. Tourette's Action [www.tourettes-action.org.uk] lists only seven endorsed NHS behavioural therapists for young people with TS throughout the UK. In England, this equates to one therapist for 10,000 children and young people with TS. This lack of provision is compounded by uneven

geographical distribution of therapists (most are located in London and the South East of England), resulting in further inequity of access, requiring long distance travel to national specialist centres which is expensive, disruptive and time-consuming for young people and their families.

Over the last decade, internet-delivered cognitive behaviour therapy (iCBT) has been developed which enables us to offer less therapist intensive, but effective, interventions over long distances, which can increase the availability of evidence based treatments. iCBT was initially shown to be an effective method in the treatment of adults with depression and anxiety disorders (Johansson and Andersson, 2012, Hedman et al., 2012).

Recently, the Karolinska Institutet, Sweden, have developed the therapist-guided 'BiP iCBT' platform for children and young people. The platform has been used to deliver iCBT for a range of different conditions, including phobias (Vigerland et al., 2013), anxiety (Vigerland et al., 2016), and obsessive-compulsive disorder (Lenhard et al., 2014). The BiP system is delivered via a secure internet platform that enables presentation of different treatment content to different patient populations. Patients log in via personal user names and passwords to access the treatment content. The iCBT treatment content is presented in chapters, like a self-help book.

This model of therapist-supported iCBT is similar to that already used in the NHS in England, in the Improving Access to Psychological Therapies (IAPT) programme, where graduate mental health workers support adult patients in use of iCBT packages for mild-moderate depression, anxiety and obsessive-compulsive disorder. However, the evidence available for the BiP system has all been conducted in Sweden and we have limited experience of delivering therapist supported iCBT to children and adolescents in the UK.

6.2 CLINICAL DATA

For many years, antipsychotics and noradrenergic agents were considered the first line treatment for tics. Although there is randomised controlled trial (RCT) evidence of short-term effectiveness of these drugs for treating tics, these drugs are often associated with significant adverse effects (see Hollis et al., 2016 for review) and now current European guidelines are recommending the use of BT as first-line treatment for tics in a stepped-care approach (Verdellen et al., 2011a).

The effectiveness of behavioural therapy for reducing tics has been well established (Hollis et al., 2016), with systematic reviews demonstrating a similar magnitude of effect for HRT/CBiT (comprehensive behavioural intervention) compared to pharmaceutical interventions (Whittington et al., 2016, Hollis et al., 2016). The aim of therapeutic interventions is to improve symptoms through treatment with a therapist. Commonly used interventions include: *habit reversal training (HRT),* whereby patients are taught to implement an action referred to as a competing response when a premonitory urge to tic is experienced; *exposure and response prevention (ERP),* where patients tolerate premonitory

urge sensations and learn from their therapist how to resist their tics. The largest trial used a program referred to as c*omprehensive behavioural intervention for tics (CBIT),* which includes HRT and adds additional elements of relaxation training, functional analyses (identification of situations which could exacerbate tics) and social support. A meta-analysis conducted by (Hollis et al., 2016) showed clear evidence of effectiveness for HRT/CBIT treatments for tics. Additionally, although there was a lack of RCT evidence for ERP, the evidence from available studies suggested both HRT and ERP may be equally effective in reducing tics. One study, compared HRT with ERP for children with tics and found no difference in the reduction of symptoms as measured by recording tic frequency and a slight tendency to favour ERP on the Yale Global Tic Severity Scale (YGTSS) (Verdellen et al., 2011a). The effectiveness of these behavioural interventions in conjunction with the lack of side effects are clear benefits of BT. However, there are a lack of trained therapists across many European countries, leaving many patients unable to access appropriate BT. Qualitative analysis collated from interviews with 42 young people with TS and a survey of 295 parents of children with TS identified that many families felt healthcare professionals were not knowledgeable about TS. Specifically, respondents noted the struggle to access limited behavioural therapy resources, with 76% of parents saying they would want behavioural therapy to be available for their child, highlighting the need for improved access to behavioural interventions for TS (Cuenca et al., 2015).

Across diagnostic conditions, studies have not only shown efficacy of iCBT compared to no-treatment control conditions, but meta analyses comparing face-to-face delivered CBT with iCBT has also demonstrated results comparable to face-to-face treatment in terms of symptom reduction (Andersson et al., 2014, Hedman et al., 2012), which could also result in 50% cost savings (Hedman et al., 2012). However, therapist guidance during iCBT has been shown to be an important contributing factor to determining outcome. Although self-guided iCBT is superficially attractive, given the very low costs of implementation, research evidence demonstrates very low adherence rates, with therapist-guided iCBT having significantly greater clinical- and cost-effectiveness (Johansson and Andersson, 2012, Cuijpers et al., 2011).

There are some clinical data to support the use of the BiP system (therapist guided iCBT). A randomised controlled trial (RCT) using the BiP system compared participants who received BiP OCD therapy with a waiting list control and found a significant reduction in OCD symptoms 3-months post-treatment (Lenhard et al., 2014). Additionally, there were no adverse events reported and participants were generally satisfied with the delivery of treatment, with only 4% stating they would have preferred face-to-face therapy. The qualitative (interview) findings from this trial revealed that participants were supportive of the online delivery of the therapy. Specifically, they noted that iCBT allowed them to control the pace and intensity of the therapy, and facilitated self-disclosure, whilst still allowing them to feel supported by a clinician (Lenhard et al., 2016).

Symptom reduction was also noted in an RCT using the BiP system for anxiety (Vigerland et al., 2016) and in a pilot study using BiP for specific phobia (Vigerland et al., 2013). These findings support the use of therapist guided iCBT using the BiP system, however, there is little research evidence with regards to the effectiveness of iCBT and TS. In a recent review of digital health interventions, Hollis et al. (2017) found the majority of interventions have been designed to help children and young people at risk for developing, or with a diagnosis of an anxiety and/or depression, with areas such as TS being largely overlooked. Innovations in BT for tics include delivery of CBITs treatment remotely via video over internet with a therapist. Two pilot RCTs have compared remotely delivered CBITs to traditional face-to-face delivery in children with TS. Results showed significant tic reduction for both groups, with no difference between the modes of delivery (Himle et al., 2012, Ricketts et al., 2016). The method of delivering CBIT was rated as highly acceptable by the participants (Himle et al., 2012).

Another innovation is the remote delivery of treatment with low level therapist involvement. The pilot study delivered in Sweden, upon which this current trial is based, compared tic reduction in children aged 8-16 years randomised to receive either ERP or HRT treatment delivered online via the BiP platform (manuscript in preparation). Participants in both groups showed improvement 3-months after treatment completion, but only participants in the ERP arm showed significant reduction on the YGTSS. Although not a powered-study, the findings show that ERP treatment delivered online via BiP may be effective in reducing tics. Furthermore, the study reported no severe adverse events. There were no drop-outs and no data loss at any of the assessment points, and 83% of parents and children rated the treatment as good or very good, indicating the trial was highly acceptable to patients in Sweden.

6.3 RATIONALE AND RISKS/BENEFITS

In summary, there is reasonable RCT evidence to support the clinical effectiveness of BT for treating children and young people with tics. The findings demonstrate equal effectiveness to pharmaceutical interventions, without the associated side-effects of medication. Qualitative data from parents and clinicians highlight the lack of resources available to provide BT to all patients and evidence-based behavioural interventions for tics cannot foreseeably be delivered at sufficient scale in the NHS with the existing number of expert therapists. iCBT is an intuitively attractive alternative method to deliver BT, with evidence showing comparable treatment effects to face-to-face delivered interventions. However, we have limited experience of delivering therapist supported iCBT to children and adolescents in the UK, with the majority of research evidence coming from Sweden and from other conditions outside TS. There is evidence that uptake and use of digital health interventions (such as BiP Tic) is highly context dependent (Lau et al., 2016, Kaplan et al., 2010) and it

would therefore be unwise to assume that a delivery package that works in Sweden will work equally well in the UK.

The aim of this study is to evaluate the clinical and cost -effectiveness of BiP Tic: a therapist-guided, parent-assisted behavioural therapy intervention programme for tics in young people with TS. The intervention will be delivered remotely via the BiP technical platform. Our primary hypothesis is that the BiP Tic remote digital behavioural intervention will be superior to a comparator intervention of online tic-related psychoeducation in reducing tics, as measured by the masked assessor-rated Yale Global Tic Severity Scale (YGTSS) total tic severity score [9]. The study design is via a single-blind parallel-group randomised controlled superiority trial, with an internal pilot and strict "stop-go" progression criteria.

This study aims to address this behaviour therapy treatment gap for young people with TS in a cost-effective manner that can be feasibly rolled out across the NHS. As the therapist role in therapist-guided iCBT is to encourage uptake and adherence to the programme, not to deliver highly specialised therapy, the skill-set required is easily acquired, as demonstrated by the successful low intensity IAPT programme, which uses graduate mental health workers to facilitate use of self-help materials by patients. Hence, if the acceptability and efficacy of the proposed therapist-guided behavioural intervention for tics is demonstrated in this trial, it should be feasible to roll-out and adopt at scale in the NHS, improving access to BT for children and young people with tics.

6.4 ASSESSMENT AND MANAGEMENT OF RISK

The following are identified as potential risks in this project:

Consent: All participants will provide written informed consent before completion of screening measures. For young people under 16-years-old we will ask for parents/carers to sign a consent form and obtain verbal or written assent from the young person. At 16 years of age or over we shall ask for written consent from the young person and their parent/carer, as both will be involved in the intervention. The informed consent form will be signed and dated by the participant (and/or his/her parent) before they enter the trial. The researcher will explain the details of the trial and provide a Participant Information Sheet. The researcher will answer any questions that the participant has concerning study participation. The information sheets have been developed with our PPI group and contain the contact information for the research team; families will be encouraged to ask the research team any questions. Where the participant is a child (under 16-years-old) an age appropriate Participant Information Sheet will be provided. In the event of any conflict between the parent and child, the child WILL NOT enter the study. The study will also be explained to the participants at the screening telephone call to ensure that participants are informed on the study procedure before attending a face-to-face screening assessment. The researcher will explain the aim, methods, benefits and hazards of participating. Risk level: Low.

New safety information: This is a low risk study, it is unlikely there will be any new safety information. Any new information will be given to the DSMB for consideration and information sheets/consent forms will be updated accordingly. Risk level: Low.

Adverse events: The process for reporting and managing adverse events has been well documented in section 18 – 'recording and reporting of adverse events and reactions'. All participants will be followed post intervention. Risk level: Low.

Withdrawal: Participants are informed in the information sheet that they may withdraw from the study at any time point. To withdraw they must contact a member of the research team. The research team will send a letter to inform them of their withdrawal, this will be recorded on the database to ensure no further contact is made to the participant. Risk level: Low.

Failure to protect privacy: All members of the research team will have undergone GCP training. No personal information will be sent to the research team prior to receiving a 'consent to contact' from either self-referral or passed on by the clinical team after consent from the patient. The BiP/BASS system is designed so only relevant members of the trial team can see outcome measures of their participants. Participant data will be identified by their study ID number. A two-factor authentication is used to log in to these systems. Both BiP and BASS also have a fine-grained privilege-system which ensures that administrators and assessors/therapists only can view information and edit settings that pertain to their role in a research project. Data sent between the platforms is encrypted and both systems have very secure firewalls. Further details on this can be found under the section "data collection and handling. Personal information linked to the study ID number will be kept in a secure file, separate from the research data. Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method). For publishing and presenting data, only anonymised group level data will typically be presented. All video data will be encrypted and stored on secured hard drives which are approved by the trial Sponsor. Further details can be found under the section "data collection and handling". Where quotes are shown from qualitative interviews, these will be identified by an anonymous code and any reference to places/names will be removed. If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly. This will be stipulated in Participant Information Sheets. Risk level: Low.

Violation of eligibility: Participants will undergo an initial screen (over the telephone) and a face-to-face screen. Researchers will be given a checklist of eligibility requirements and will be encouraged to discuss any concerns with the trial manager or CI. All researchers will be fully trained. Risk level: Low.

Risk of harm: It is unlikely that participants will experience any adverse events during this trial as a result of the intervention. Adverse events will be monitored throughout the trial; there

will be close liaison between the participant and the therapist throughout the trial so that any adverse reactions can be noted. Likewise, mid-way through the treatment the researcher will also administer a formal check on adverse events. All adverse events will be recorded on CRFs and reported to the Sponsor, DSMB and the CI. Further details on stopping rules can be found under Section 11.2 'Discontinuation/Withdrawal of Participants and Stopping Rules'.

All participants that experience an adverse event will be followed-up until the event is resolved. Where necessary, the participant's GP will be informed about the event. Risk level: Low.

Therapist does not support the intervention effectively: The therapists will be trained by experts how to deliver the intervention and will be supervised by two experienced tic specialists (London and Nottingham). Therapists will receive guidance in the form of intervention protocols and manuals. Throughout the trial there will be close contact between the research team and the therapists to ensure adherence to protocol. Risk level: Low.

The behavioral therapy: iCBT differs from traditional therapy in the amount of information that the therapist gives to the participant on a session-by-session basis. A thorough assessment decreases the risk of patients in need of more extensive care (e.g. risk management) being included in the study. The regular e-mail communication, and the possibility for the participating families to contact their therapist if needed, ensures that families with problems too severe for this program will be referred to more suitable treatments. Additionally, if the child is considered to be a risk to self or others they are not considered eligible for the trial and will remain under the care of their local clinical team. Risk level: Low.

The comparator (online education): In our view, the ethical risk is limited since every study participant will receive treatment. Participants in the comparator arm will not receive the iCBT intervention, and instead will receive tic education. Although we believe this will not be as effective as iCBT in reducing tics, it will offer some therapeutic benefits, indeed, tic education is provided in all behavioural interventions and has been used previously in other RCTs in TS (Piacentini et al, 2010; Yates et al, 2016) iCBT intervention. Given that the majority of children/young people do not receive access to any form of BT, we believe that the intervention delivered as the control will still be outweigh any benefit of standard care (which is typically no therapeutic intervention). However, in both arms (the intervention and control group), participants are permitted to continue on any tic medication and thus both groups will be receiving support for their tics, over and above standard care. Additionally, as noted above, if the family's problems are too severe for this trial or the child is considered to be a risk to self or others they are not considered eligible for the trial.

Risk associated with other medical conditions: There should be little risk in relation to other medical conditions. Information on other conditions is collected at screening, if there are

concerns about participation the CI will make the ultimate decision to include them in the trial. The participant's GP will be informed of their participation. Risk level: Low.

Training of researchers: All staff will be GCP trained. All research staff will be trained in administering research assessments, including Yale Global Tic Severity Scale. Yale assessments will be recorded and checked for accuracy at set time intervals. Risk level: Low.

Recruitment and adherence to protocol: Recruitment and adherence to measure completion will be assessed 9-months post start of recruitment to ensure that it is feasible to recruit into the study. Should the trial not meet the pre-specified stop/go criteria the TSC will consider terminating the trial. The young age of the population may make recruitment and adherence more challenging. We will manage this risk by involving the parent on the consenting process. We have also developed the study design, information sheets and intervention with help from PPI members, including children and young people with tics, to ensure the intervention is 'user-friendly' and meets the needs of the target population. Furthermore, both groups receive an active intervention, therefore, there should be no difference in the participants' motivation to complete measures based on their arm allocation. Risk level: Low.

Trial conduct: There are good management procedures in place, including TSC/DSMB and an experienced Project Management Group. The trial is also supported by Priment CTU which is overseeing trial management, providing SOPs and keeping track of training logs for research teams and the staff at research sites. There are appropriate regular team meetings in place with communication via telephone or email where necessary. The research team will keep in weekly contact with the sites (including PIC sites). All sites and researchers will be trained on the research process. As this is a single blind study, there is a small risk that assessors may become unblinded. We will minimise this risk by the following: assessors will remind participants at each stage that they must not discuss their intervention with their assessor; both groups receive an intervention of similar length, supported by similarly trained therapists, delivered through the same platform and receive the same measures; details of treatment are stored in BIP, which assessors cannot access, measures are completed via BASS; if an assessor does become unblinded we will make a note of this and ask an alternative assessor to complete future outcome measures for this participant. Risk level: Low.

7 OBJECTIVES

Primary: To evaluate the clinical effectiveness of BiP Tic: a therapist-guided, parent-assisted behavioural intervention programme for tics in young people with Tourette syndrome and chronic tic disorder, compared with usual care plus online education.

Secondary:

1. To optimise the design and delivery of BiP Tic in partnership with young people with TS, carers and healthcare professionals (HCPs) to maximise acceptability, effectiveness and long-term uptake.
2. To undertake an internal pilot to assess whether recruitment, engagement with the intervention and retention to the trial are sufficient to allow the trial to progress and provide a definitive answer on effectiveness.
3. To evaluate the cost-effectiveness of BiP Tic.
4. To estimate the longer-term impact on patient outcomes and NHS costs.
5. To identify the barriers and facilitators to implementation from the perspective of patients, parents, healthcare professionals (HCPs), managers of NHS Services and commissioners.

8 OUTCOMES

8.1 PRIMARY OUTCOMES

The primary outcome for this study is the severity of tics as measured by the total tic severity score (TTSS; 0-50) on the Yale Global Tic Severity Scale (YGTSS; (Leckman et al., 1989)). The primary end point is 3-months post-randomisation. The primary outcome measure (YGTSS) will be measured at baseline (pre-intervention), 3-months (primary end point), 6, 12 and 18-months post randomisation.

The YGTSS is administered by a blinded assessor as an investigator-based semi-structured interview focussing on motor and vocal tic frequency, severity and tic related impairment over the previous week. The YGTSS symptom checklist lists 46 tic disorder symptoms, including 12 simple motor tics (e.g., eye blinking), 19 complex motor tics (e.g., facial expressions), seven simple vocal tics (e.g., coughing), and eight complex vocal tics (e.g., words), with four of these items designated on the instrument as “other” symptoms. The YGTSS generates a total tic severity score (0-50) and an impairment score (0-50).

Five index scores are obtained: Total Motor Tic Score, Total Phonic Tic Score, Total Tic Score, Overall Impairment Rating, and Global Severity Score. The Total Motor Tic Score is derived by adding the five items pertaining to motor tics (range: 0–25); the Total Phonic Tic Score is derived by adding the five items pertaining to phonic tics (range: 0–25); the Total Tic Score is derived by adding the Total Motor Tic Score and the Total Phonic Tic Score; and the Overall Impairment Rating is rated on a 50-point scale anchored by 0 (*no impairment*) and 50 (*severe impairment*). A Global Severity Score is derived by summing the Total Motor Tic Score, Total Phonic Tic Score, and Overall Impairment Rating (range: 0–100). The Total Tic Score (0 - 50) is the primary outcome. The YGTSS takes between 15 to 35 minutes to administer (longer time at baseline with quicker follow-ups).

The baseline assessment will be conducted face-to-face. When possible, the follow-up assessments (3, 6, 12 and 18 months post-randomisation) will be conducted by the same

blinded assessor via video-conference call/WebEx or telephone. At each time point, the assessors will use our self-made YGTSS Excel-grid to make notes on what information the rating of each item was based.

A clinical expert (Dr Tara Murphy) will conduct a workshop with the assessors which will include background education to each item. The assessors will then be asked to rate some videos of previous YGTSS interviews. The videos are already recorded with permission of the patient. Following training, inter-rater agreement and inter-rater reliability will be established for assessors using the YGTSS. We will ask the participants permission to record all YGTSS assessments, for possible spot checks of the methodology and to measure reliability of the primary outcome measure.

8.2 SECONDARY OUTCOMES

Parent Tic Questionnaire (PTQ) (Chang et al., 2009): The PTQ assesses the number, frequency, and intensity of motor and vocal tics in children and adolescents with tics. The questionnaire contains two separate lists, one of 14 common motor tics, one of 14 common vocal tics. For each tic recorded as present, parents/carers indicate the frequency and intensity of that tic. Frequency ratings are made on a 1-4 scale (constantly, hourly, daily, and weekly) and intensity ratings are made on a 1-4 scale. A separate score for each tic is calculated by adding the frequency and intensity ratings, giving a score ranging from 0-8. Motor and vocal tic severity scores are computed by summing the scores for all motor and vocal tics respectively and a severity score computed by summing the two sub-scores. The questionnaire has established validity and reliability (Chang et al., 2009). The PTQ will be completed by parents/carers at all measurement time points (baseline, mid-treatment, 3, 6, 12 and 18-month follow-up) via the BASS platform (online). The questionnaire takes less than 10 minutes to complete.

Yale Global Tic Severity Scale YGTSS – Impairment scale (Leckman et al., 1989): The impairment scale forms part of the YGTSS described above. The impairment rating is on a 50-point scale anchored by 0 (*no impairment*) and 50 (*severe impairment*). The rating focuses on distress and impairment experienced in interpersonal, academic, and occupational realms. Further details can be found under the description of the primary outcome.

Clinical Global Impressions Scale (CGI)-Improvement (Guy, 1976): The CGI provides an overall clinician-determined summary measure that takes into account all available information, including a knowledge of the patient's history, psychosocial circumstances, symptoms, behaviour, and the impact of the symptoms on the patient's ability to function. It is being used in this trial to provide an assessor-rated opinion of global improvement. The CGI comprises two companion one-item measures evaluating the following: (a) severity of psychopathology from 1 to 7 and (b) change from the initiation

of treatment on a similar seven-point scale. For the purpose of this study, only the CGI-Improvement (CGI-I) will be recorded. The CGI-I consists of one item: "Compared to the patient's condition at admission to the project [prior to medication initiation], this patient's condition is: 1=very much improved since the initiation of treatment; 2=much improved; 3=minimally improved; 4=no change from baseline (the initiation of treatment); 5=minimally worse; 6= much worse; 7=very much worse since the initiation of treatment." The questionnaire has established validity and reliability (Busner and Targum, 2007) and will be completed online via the BASS platform at each follow-up time point after treatment (3-, 6-, 12-, 18-months) by the researcher who completes the YGTSS. The CGI form can be completed in less than a minute by an experienced rater.

Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983): The CGAS is a 0-100 scale that integrates psychological, social and academic functioning in children as a measure of psychiatric disturbance. It is being used in this trial to provide an assessor-rated opinion of global improvement. The instrument provides anchor point descriptions of behavioural functioning across different life situations for each decile. Scores above 70 indicate functioning in a normal range. The questionnaire has established validity and reliability (Green et al., 1994). The CGAS will be completed by the researcher who completes the YGTSS via the BASS platform (online) at baseline, 3-, 6-, 12- and 18-month follow-up. The CGAS can be completed in less than a minute.

Strengths and Difficulties Questionnaire (SDQ – parent completed) (Goodman, 1999). The SDQ is a brief measure of behavioural and emotional difficulties that can be used to assess mental health problems in children and young people aged 4-17 years. The SDQ consists of 25-items that are rated on a 3-point Likert scale (not true, somewhat true, and certainly true), with a mixture of positive and negatively phrased items. The items are designed to be divided between five sub-scales, each consisting of five items, which can be used to create scores for: emotional symptoms, conduct problems, hyperactivity-inattention, peer problems and pro-social behaviour. The items for all but pro-social behaviours can be summed to generate a 'total difficulties score'(Goodman, 2001). The standard SDQ can be supplemented with a brief impact supplement which assesses the impact of the child's difficulties in terms of distress, social impairment, burden and chronicity (Goodman, 1999). The questionnaire has established validity and reliability (Goodman, 1999). The SDQ will be completed by parents as part of the Development and Wellbeing Assessment (DAWBA) at baseline and via the BASS platform (online) at 3-, 6-, 12- and 18-month follow-up. The SDQ takes approximately 5-10 minutes to complete. It is being used in this trial to measure any differences across different symptom domains (and the impact of these symptoms) between the two study arms.

The Mood and Feelings Questionnaire (MFQ; Child completed version) (Angold et al., 1995) is a 33-item questionnaire designed for children and adolescents 6–17 years old to report depressive symptoms as specified by the DSM-III-R diagnostic criteria for major

depression. It also includes neuro-vegetative symptoms and feelings of loneliness, being unloved and ugliness. The items are rated on a 3-point scale (0=not true, 1 = sometimes, 2 = true). The MFQ is scored by summing together the values for each item. The questionnaire has established validity and reliability (Burleson Daviss et al., 2006). The MFQ will be completed by the child/young person at each time point (baseline, mid-treatment, 3-, 6-, 12- and 18-month follow-up) via the BASS platform (online). Where necessary, the parent/carer can assist the child/young person in completing the MFQ. The MFQ takes less than 10 minutes to complete. The measure is being used to assess any differences in low mood between the two study arms. It is being completed at mid-treatment as an additional check for potential side-effects.

Spence Child Anxiety Scale SCAS (self-report)(Spence, 1998). The SCAS is a child self-report measure designed to evaluate symptoms relating to separation anxiety, social phobia, obsessive-compulsive disorder, pain, agoraphobia, generalised anxiety and fears of physical injury. The measure is being used to assess any differences in anxiety between the two study arms. The SCAS consists of 44 items, of which 38 reflect specific symptoms of anxiety and 6 relate to positive filler items to reduce negative response bias. Children are asked to rate on a 4-point scale (never=0, sometimes=1, often=2, always=3) the frequency in which they experience each symptom. The ratings are summed from the 38 anxiety items to provide a total score (max=114), with high scores reflecting greater anxiety. The questionnaire has established validity and reliability (Spence, 1998). The SCAS will be completed by the child/young person at baseline, 3-, 6-, 12- and 18-month follow-up via the BASS platform (online). Where necessary, the parent/carer can assist the child/young person in completing the SCAS. The SCAS takes less than 15 minutes to complete.

Child Health Utility 9D (CHU9D; parent and child completed versions) (Stevens, 2010). The CHU9D is a pediatric quality of life measure for use in health care resource-allocation decision making. The CHU9D can be used in children as young as 7-years-old. The questionnaire consists of 9 items each with a 5-level response category. Each item taps into a different domain (worry, sadness, pain, tiredness, annoyance, school, sleep, daily routine and activities). The time frame for the questions is “today”. There are two versions of the questionnaire, a self-report measure and a proxy measure which can be completed by the parent/carer of the child. The questionnaire has established validity and reliability (Furber and Segal, 2015). The CHU9D will be completed at baseline, 3-, 6-, 12- and 18-month follow-up via the BASS platform (online) by the parent/carer and the child/young person as a global measure of quality of life. The questionnaire takes less than 5 minutes to complete.

The Child and Adolescent Gilles de la Tourette Syndrome–Quality of Life Scale (C&A-GTS-QOL) (Cavanna et al., 2013). The C&A-GTS-QOL is a disease-specific measure of health-related quality of life designed for children and adolescents with TS. There are two

versions of the measure, one for children aged 6-12-years and one for young people aged 13-18-years. The questionnaire consists of 27-items each with a 5-level response category. The items are broadly the same for both versions with slight changing of words for age-appropriateness. The scale consists of four subscales (psychological, physical, obsessive-compulsive, and cognitive). The time frame for the questions is "The last four weeks". The English version of the questionnaire has established acceptability, validity and reliability (Su et al., 2017). The GTS-QOL will be completed at baseline, 3-, 6-, 12-, and 18-month follow-up via the BASS platform (online) by the child/young person as a disease-specific measure of quality of life. Where necessary, the parent/carer can assist the child/young person in completing the GTS-QOL. The questionnaire takes 5 minutes to complete.

Client Service Receipt Interview (CSRI): (Beecham and Knapp, 2001) The CSRI is a flexible research instrument developed to collect information on service receipt, service-related issues and income. The questions of the CSRI are largely structured with a multiple-choice format but, to contend with the complexity of community care arrangements, a few open-ended questions are also asked. The measure also asks about school attendance since the last measure completion time point (3/6 months). A modified version of the CSRI will be completed at baseline, 3-, 6-, 12- and 18-month follow-up via the BASS platform (online). This modified version also combines elements of the Child and Adolescent Service Use Schedule (CA-SUS) (Byford et al., 2007)The questionnaire takes less than 15 minutes to complete.

Adverse events (Side effects): Adverse events/side effects will be recorded on a modified version of the side effects scale developed by (Hill and Taylor, 2001). The scale consists of 17 short items relating to common side effects (such as headaches, anxiety, sleep, and low mood). The participant is asked to respond on a 5-point scale ranging from "not at all" to "all the time" to describe the presence of each item. Item 17 asks if the patient has tics, this has been modified to read "increased tics" as tics will be present in our sample. The adverse events/side effects scale will be completed at baseline (to ascertain presence of these symptoms prior to treatment), mid-treatment and 3- and 6-month follow-up via the BASS platform (online) by the parent/carer with input from the child/young person. The questionnaire will take less than 5 minutes to complete.

Treatment credibility: To assess treatment credibility, we will administer a modified version of short questionnaire created by the research team and used in the previous BiP pilot study. The questionnaire consists of 2-items which are scored on a 5-point scale. The questionnaire asks how well the internet treatment suits children for managing tics, and how much improvement they expect from the treatment. The questionnaire will be completed 3 weeks into the treatment by parents/carers and children/young people via the BASS platform (online). The questionnaire will take less than 5 minutes to complete.

Treatment satisfaction and need for further treatment: To assess treatment satisfaction, the research team have modified a brief 7-item scale that was previously used in the BiP pilot study. Six of the 7-items are scored on a 5-point scale and ask how helpful the treatment was, and would they recommend it to others. The 7th item is a three choice option asking if the families would prefer face-face treatment, no preference, or internet treatment. The need for further treatment questionnaire consists of 1 item that asks the children/young people and parents/carers and to rate if they feel they/their child needs more treatment for their tics. This is rated on a 5-point scale ranging from "I/my child doesn't need any more treatment" to "I/my child needs a lot more treatment". Both the satisfaction and need for further treatment questionnaire will be completed at the 3-month follow-up point via the BASS platform (online) by parents/carers and children/young people. Both questionnaires will take less than 5 minutes to complete in total.

Concomitant interventions: To assess what other treatments/interventions the child/young person is accessing during the study period, parents will be asked to complete a short questionnaire which asks about current diagnoses and treatments/interventions/ medication in progress. This will be completed at baseline as part of the demographic questionnaire completed with the researcher, and then again at 3-, 6-, 12-, and 18-month follow-up with the researcher via WebEx/telephone prior to conducting the YGTSS. The questionnaire will take less than 5 minutes to complete.

Process Evaluation: The process evaluation will follow the MRC guidelines for evaluating the implementation of complex interventions. It will explore the implementation of intervention (i.e. quality and quantity of what is delivered during the trial): the structures, resources and processes through which delivery is achieved, and the quantity and quality of what is delivered. It will also assess the fidelity of the interventions and make recommendations for adaptations. Finally, it will examine the potential mechanisms underlying behaviour participant change and probe for unexpected consequences. As this study has an active control and to minimise the risk of unblinding researchers collecting the outcome measures we will interview children and parents in both the intervention and the control condition.

Interviews will be conducted with therapists supporting the intervention (Target n>5), clinicians recruiting to the study, children in the intervention or control arms (n=>20 in each arm) and parents of children in the intervention arm (n=>20 in each arm). Four semi structured interview schedules will be prepared and piloted with relevant stakeholders. Therapist and clinician interviews will be commenced during the first three months of intervention delivery. Parent and child interviews will commence after the child has completed the three month outcome measures. The therapists' interviews will explore their perceptions of delivery of support including skill set and training required to support use of BiP Tic, fidelity of delivery of BiP Tic, benefits and problems encountered by

children, adolescents and their parents using BiP Tic, contextual factors influencing delivery and uptake of BiP Tic and barriers to implementation and potential solutions to problems identified. Clinicians' interviews will explore the acceptability of the BiP Tic intervention, how BiP Tic could best be incorporated into routine NHS practice, including how to maximise uptake and use by patients (i.e. service redesign), how use of BiP Tic should be addressed in commissioning and funding flows and the potential reach of the intervention.

Parent and child interviews will explore satisfaction with BiP including in relation to other treatments where applicable; usability; acceptability and uptake of online resource; acceptability and uptake of therapist support; contextual factors influencing uptake and acceptability; barriers to implementation; suggestions for modifications and solutions to problems identified.

As part of the BiP system, the following measures are also recorded: Total therapist time; therapist time specified for each therapist; therapist time specific to each child or parent; total number of characters submitted (as part of communication messages via the BiP system); total number of logins for child or parent; average time between each login (in days), for child or parent; average pages visited per login, for child or parent; and the five most frequently visited pages per child or parent. Participants can also practice stopping their tics using a stopwatch function inbuilt into the BiP system. This collects ratings of premonitory urges.

Qualitative data will be analysed using thematic analysis (Braun and Clarke, 2006) and a mixed methods approach will be used to integrate qualitative and quantitative data.

8.3 SAMPLE SIZE AND RECRUITMENT

8.3.1 SAMPLE SIZE CALCULATION

To detect a clinically important average difference of 0.5 of a standard deviation between intervention and comparator with 90% power at $p<0.05$ (2-sided), after making an allowance of 20% for dropout, requires a total sample size of 220 participants. Our systematic review (Hollis et al., 2017) found the average estimate for the standard deviation (SD) of the YGTSS (TTSS) from 19 trials of behavioural intervention for tics was 6.6. Thus, the trial is powered to detect an average change of 3.3 on the YGTSS, which should be sufficient to ensure the risk of missing a clinically significant effect in the trial is low.

8.3.2 PLANNED RECRUITMENT RATE

Recruitment is planned to be conducted within an 18 month Period. Our sample size calculations show we need to recruit 220 participants. With a recruitment period of 18 months, this equates to an average of 12.2 participants per month. As there is often a

lag period at the beginning of recruitment, where staff in clinics are still getting used to the recruitment procedures and our national advertising campaign takes full effect, we anticipate a slower start to recruitment. Thus, for the first nine months of the trial we expect somewhere between 3 and 14 participants recruited into the trial each month (with the number increasing each month). If 66 participants have not been recruited by the end of the internal pilot (9 months after recruitment commences: December 2018) the TSC will consider terminating the trial. After the first nine months we anticipate recruitment will be between 10 and 18 participants enrolled in the trial each month.

We are not aware of any other competing studies that are in progress or planned that would affect recruitment. Input received from young people and carers in developing this trial indicates that participation in the trial will be attractive as it guarantees access to a behavioural intervention, which is frequently requested but often unavailable. The design will also be attractive as all participants will get access to some form of intervention (behavioural therapy or online education).

Furthermore, our national recruitment network of specialist clinics; including multiple community CAMHS and paediatric clinics and the national charity Tourette's Action has the capacity to meet the recruitment target within the time window.

Our likelihood of achieving our target was based on the following: during the recruitment window our two study sites will see 140 eligible new referrals. There will be approximately 40 existing eligible patients at the two sites. We have confirmed Patient Identification Centres (PICs) recruiting into the trial, each estimate a conservative minimum of 10 patients who consent and enrol into the trial (PIC total enrolled = 150-180). Based on the membership of Tourette's Action and our eligibility criteria, we expect to be able to identify 80 consenting/enrolled participants from the Tourette's Action website as a conservative estimate.

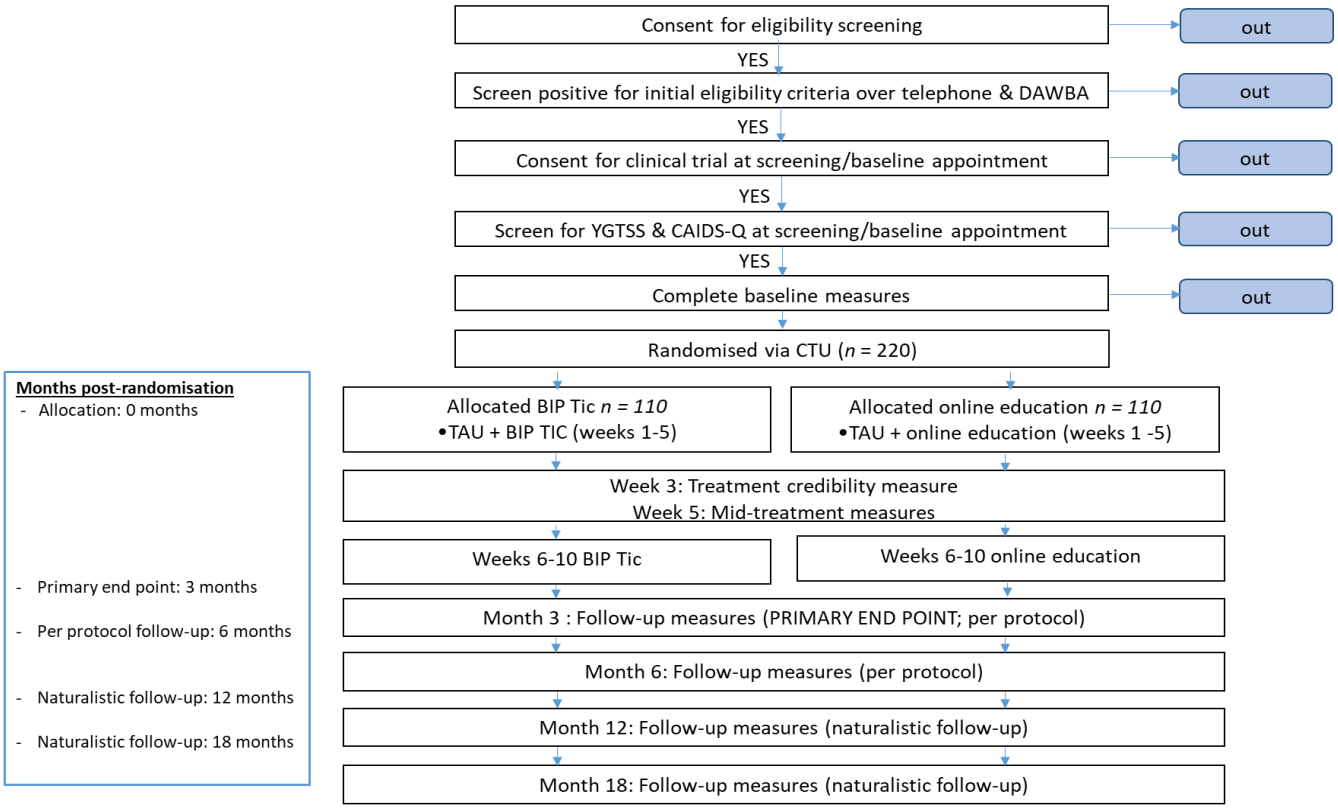
9 TRIAL DESIGN

9.1 OVERALL DESIGN

A 10-week, parallel-group, single blind, non-commercial, randomised controlled superiority trial with an internal pilot for children and young people with tics. Participants will be randomised to receive 10-weeks treatment of either online, remotely-delivered, therapist-supported behavioural therapy for tics or online, remotely-delivered, therapist-supported education on tics. The 10-week intervention period was selected based on the length of an established intervention (BiP Tic) which has been piloted in Sweden. Participants will be randomised in a 1:1 ratio to behavioural therapy or online education. Randomisation will be stratified by site (Nottingham and London) and conducted online via Sealed Envelope with blinding of researchers/outcome assessors. All participants receive the same outcome measures

so assessors will not know which group the participant is in by the measurements. Participants will be reminded by their assessor that they are not to disclose arm allocation to them. If an assessor becomes unblinded, subsequent assessments for that participant will be conducted by a different assessor (blind to arm allocation) where possible. Participants will be followed-up at mid-treatment, 3-, 6-, 12-, and 18-month post-randomisation. The choice of an 18-month follow-up was selected in line with the NIHR HTA call (16/19) requesting that participants be followed-up at this time point. Months 3 and 6 are an 'intention to treat' follow-up in which participants are encouraged not to change medication or start alternative therapies for tics. Months 12 and 18 are a naturalistic follow-up where participants may be using alternative treatments in accordance with standard practice recommended by their usual treating clinician. A sub-sample of participants and parents will be purposively selected to participate in Process Evaluation interviews after the 3-month follow-up time point. Children will be selected to maximise diversity of age, gender, ethnicity, TS severity and engagement with intervention. A flow chart of the study design is shown in Figure 2.

Figure 2: Schematic diagram of overall trial design



9.2 RECRUITMENT

Participants will be identified and recruited by either (1) clinic staff or clinical study officers (CSOs) at PICs, (2) the two study sites (Great Ormond Street Hospital [GOSH] and Nottinghamshire Healthcare Foundation Trust [NHCFT]), or (3) via Tourette's Action (tic charity) website and a study website, including links to Tourette's Action via social media such as Twitter and Facebook. Full details on participant identification can be found in

section 11.1 (Participant Identification). All individuals conducting initial patient identification at sites will be given the inclusion/exclusion criteria for the study. All participants recruited publically via websites/Tourette's Action will also be provided with brief eligibility criteria for the study. The eligibility criteria are outlined in section 10 (Selection of Participants). Patients who provide 'consent to contact' (C2C) will be contacted by a member of the research team who will explain the study process and ascertain some screening eligibility over the phone to determine the presence of any obvious exclusion criteria (see section 11.1 for further details).

The following information will be collected at each stage:

Information collected at PIC and study sites: Clinicians/CSOs at PIC and study sites will be asked to assign a screening number for each patient approached about the study and record whether the patient is willing to be contacted by the research team, recording the reason for non-participation. This will be passed on to the research team and will not contain any personal or identifiable information for patients who do not consent to be contacted by the research team. For participants who consent to contact, patient's contact details will be provided to the research team. Reasons for non-participation will be recorded (where given) for Consolidated Standards of Reporting Trials (CONSORT) purposes.

Information collected for self-referrals: For people who complete the self-referral 'consent to contact' via the BASS system, their contact details will be recorded as part of the consent to contact which will be seen by the research team.

Information collected during initial telephone call: After the research team receive the C2C form and contact details they will arrange a telephone screening appointment with the participant. At this point the following details will be recorded: contact details, age of tic onset and brief history of tics, previous contact with health care services, previous/current tic medications or therapy, access to internet/PC/Mac/laptop, other diagnoses, inclusion/exclusion criteria (the assessment of tic severity or intellectual disability will not be conducted at this time point as this will involve the completion of semi-structured interview which will be conducted after fully-informed consent at the screening/baseline appointment). The researcher will outline the time commitment involved in the trial at this stage. The researcher will log the screening number assigned at the PIC site, or, for cases self-referred through websites / Tourette's Action (via the BASS system), assign the patient a screening number, the method of referral and their potential likelihood to meet the inclusion/exclusion criteria. Participants meeting any exclusion criteria or not meeting any inclusion criteria at this time point will not be invited to screening. If the patient is not eligible for the study or does not wish to attend a screening appointment, the researcher will record the reason for non-participation. Reasons for not attending baseline/screening assessment will be recorded for CONSORT reporting.

Families who pass the initial telephone eligibility screen and who are willing to attend a face-to-face screening appointment will be asked to complete a DAWBA assessment online. The participant will be provided with log in details of the DAWBA. The participant will also be asked to send the link to the DAWBA (and log in details) to the child's teacher to complete the teacher DAWBA. The researcher will encourage the parent to ask the child's teacher to complete the DAWBA, but it is at the discretion of the parent if they are willing to involve the teacher. The DAWBA has been fully described under section 11.3 'Screening Period' and information on data storage is found under section 12.4 'Data collection and handling'. The parent DAWBA must be completed before the participant can be enrolled into the study. The process of collecting this information at screening is outlined in the 'consent to contact' form.

Information collected during screening appointment: Patients will be invited to attend a face-to-face screening appointment at one of the study sites (GOSH or NHCFT). Patients will be reimbursed for the travel costs regardless of whether they are subsequently enrolled into the trial. At the screening appointment, the details collected over the telephone for the patients will be checked. The participant will be consented into the trial and undertake the CAIDS-Q to ascertain presence of intellectual disability (with the assessor/researcher). They will then complete the YGTSS. The YGTSS has been fully described under 'primary outcome'. The researcher will then confirm the eligibility criteria once all screening measures are completed. Any patients not eligible or wishing to participate in the trial will be recorded alongside reason for ineligibility. Eligible participants will be asked to complete baseline measures. The participant will be given their study ID at the point of randomisation when they are enrolled into the study. A log will be kept matching screening IDs with study IDs. Randomisation will occur at or just after the screening/baseline appointment, prior to starting treatment.

This screening/baseline assessment will be conducted by a member of the research team with GCP training who will confirm the eligibility of the patient. Where possible, the same researcher who conducted the initial telephone call will conduct screening/baseline appointment. The local GP for the patient will be notified that the family has been contacted and the research team will indicate in writing whether or not the child has been recruited to the study. Reasons for not meeting eligibility criteria will be recorded for CONSORT reporting. Data recorded from participants who are not enrolled into the trial will only be used anonymously for CONSORT reporting (to record reasons for ineligibility) and will not be included in the study analysis.

The screening process is fully outlined in section 11.1 (Participant Identification) and 11.3 (Screening Period).

We plan to utilise our links with Tourette's Action to have a very engaged and active social media presence. This will fulfil two aims 1) involve and update patients and public in the trial and 2) promote recruitment to the trial. The website will be regularly updated to

publish testimonials of participant's experience of the trial, alongside updates from the research team on the status/progress of the trial. Only testimonials from those who consent will be published on the website. The main content of the website information regarding the trial will be submitted for ethical approval. SELECTION OF PARTICPANTS

Participants who meet the inclusion criteria and answer "no" to the exclusion criteria will be eligible for the trial. No deviations or waivers to the eligibility criteria are allowed. There are three main routes for selection of participants into the trial. One is through identification from participant records of previous or current patients at one of the two study sites (GOSH, or NHCFT). The second is through Patient Identification Centres (PIC) throughout England. The third is through self-referral for Tourette's Action/ study webpage. The inclusion/exclusion criteria will be made available to all clinicians at PIC/study sites and will be available to all potential participants on the relevant websites (Tourette's Action and the study webpage). Participant's eligibility will be checked by the research team at the screening/baseline assessment appointment. Further details on patient identification are found in section 11.1 (patient identification).

9.3 INCLUSION CRITERIA

1) Aged 9 to 17: patient confirmed through screening.
2) Suspected or confirmed Tourette syndrome/ chronic tic disorder:
   - Including Moderate/severe tics: Score >15 on the Yale Global Tic Severity Scale (YGTSS) Total Tic Severity Score (TTSS); TTSS score>10 if motor or vocal tics only: researcher confirms at screening appointment
3) Competent to provide written, informed consent (parental consent for child aged <16): researcher confirms at screening appointment.
4) Broadband internet access and regular PC/ laptop/Mac user, with mobile phone SMS: patient confirmed through screening.

9.4 EXCLUSION CRITERIA

1) Previous structured behavioural intervention for tics e.g. HRT/CBIT or exposure and response prevention within last 12 months: Patient confirmed through screening.
2) Change to medication for tics (start or stop tic medication) within the previous 2 months: Patient confirmed through screening and subsequent medication/interventions commenced throughout out the trial are recorded at each time point for analysis.
3) Diagnoses of alcohol/substance dependence, psychosis, suicidality, or anorexia nervosa: Confirmed through parent DAWBA. DAWBAs that score people as being likely to have these conditions will be second reviewed by the CI (who is a medical expert) to ascertain that they should definitely be excluded from the trial. If the child is considered at immediate risk of suicide, the research team will inform the GP or usual treating clinician.

4) Moderate/severe intellectual disability: Confirmed through qualitative judgement of the assessor at the telephone screen (and confirmed at baseline through CAIDS-Q) through questions relating to type of school the child attends and previous diagnoses.
5) Immediate risk to self or others: Confirmed through screening questions and DAWBA. The participants GP will be informed of this.
6) Parent or child not able to speak or read/write English: Patient confirmed through screening by the assessor.

Further details on the DAWBA, and telephone screening schedule can be found under Section 11.3 'Screening Period', on the CAIDS-Q under Section 11.6 ', an on the YGTSS under section 8.1 'Primary Outcome'.

10 STUDY PROCEDURES AND SCHEDULE OF ASSESSMENTS

10.1 PARTICIPANT IDENTIFICATION

There will be three streams to participant identification. Please also see Figure 1 under section 5 'Trial Flow Chart' for the identification process.

Stream 1: Screening of previous and current referrals at GOSH and NHCFT

A member of the usual care team (or Trust employed Clinical Study Officer; CSO) will identify participants from the patient records or current referrals held at GOSH or NHCFT. This will involve screening of identifiable personal information. The member of the clinical care team/CSO will screen the existing/previous patients using the eligibility criteria. A member of the care team will contact the patient via letter, email or phone and ask the patient if they would be potentially interested in being involved in the study. They may also discuss the study with the patient during a face-to-face consultation. Patients will be provided with a brief information sheet and 'consent to contact' form. Written confirmation of consent to contact will be recorded by the member of the clinic team or CSO. If patients provide consent to be contacted by a member of the research team, their contact details will be passed on to the research team by a member of the usual care team. This will act as their referral into the study. All consent to contacts received by the research team will be entered into the BASS system.

Stream 2: Patient identifying Centre's (PICs) – CAMHS or Community Pediatric services

A member of the usual care team (or Trust employed CSO) will identify participants from the patient records or current referrals held at the PIC site. This will involve screening of identifiable personal information. The member of the clinical care team/CSO will screen the existing/previous patients using the eligibility criteria. A member of the care team will discuss the study with the patient, usually face-to-face in their clinic appointment, but also potentially via letter, email or phone if patient records are

searched for previous patients. Patients will be provided with the brief information sheet and 'consent to contact' form. Written confirmation of consent to contact will be recorded by the member of the clinic team or CSO. If patients provide consent to be contacted by a member of the research team, their contact details will be passed on to the research team by a member of the usual care team. This will act as their referral into the study. All consent to contacts received by the research team will be entered into the BASS system.

Stream 3: Publically recruited participants through websites

Participants will also be recruited through public recruitment campaigns. Specifically, the study will be advertised for participant recruitment via two streams: Tourette's Action website (a national charity for people with tics) and a study website. Tourette's Action and the study website will host basic information about the study, in the form of the same study information provided in the brief information sheet and a 'consent to contact' form hosted on the BASS platform (included for ethical approval). Interested patients will read the information and complete the 'consent to contact' form. The consent to contact form is identical to that used by sites, only participants have to tick rather than initial the boxes. For self-referring patients this will be completed via the BASS system and the information will then be accessible to the research team. The research team will contact the patient at the point of having both a completed 'consent to contact' form. Signposting to these two websites will take place via Twitter and Facebook through the accounts of Tourette's Action and MindTech. The information posted these accounts will be in the form of: anonymous quotes and feedback about the study from participants and regular study updates from the research team about progress and status.

10.2 INFORMED CONSENT PROCEDURE

For patients who are identified for the trial by their usual treating clinician (from a PIC) initial 'consent to contact' will be obtained from the participant via their usual treating clinician. Clinicians at PIC sites or full-study sites (GOSH or NHCFT) will approach patients who are potentially eligible for the trial by providing the brief study overview sheet and consent to contact form. If patients provide consent that they are happy to be contacted by a member of the research team, a member of the patient's usual care team will provide the research team with the contact details. For patients who self-refer into the trial via Tourette's Action/websites, the completed online 'consent to contact' form will be immediately available to the researchers via the BASS platform.

All potential participants will be contacted by a member of the research team and undergo initial screening, including: initial telephone screening; complete the DAWBA if they meet

initial criteria; attend face-to-face screening/baseline assessment. This has been fully described under Section 9.2 'Recruitment'.

All participants will provide written informed consent before completion of screening measures. For young people under 16 years we shall ask for parents/carers to sign a consent form and verbal or written assent from the young person. At 16 years or over we shall ask for written consent from the young person and their parent/carer, as both will be involved in the intervention. The informed consent form will be signed and dated by the participant (and/or their parent) before they enter the trial. The researcher will explain the details of the trial and provide a Participant Information Sheet. The researcher will answer any questions that the participant has concerning study participation. The information sheets have been developed with our PPI group and contain the contact information for the research team; families will be encouraged to ask the research team any questions. Where the participant is a child under the age of 16 years, an age appropriate Participant Information Sheet will be provided. In the event of any conflict between the parent and child, the child WILL NOT enter the study.

On the consent form there will be a separate statement requesting permission to contact the family for an interview about their experiences of the study. If this box is not initialled, the family will not be considered for the qualitative interviews.

It is the responsibility of the researcher to obtain written informed consent from each participant prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. The person taking consent will be GCP trained, suitably qualified and experienced, and have been delegated this duty by the CI on the delegation log.

All participants will have at least 24 hours from receiving the initial study information to signing consent. The participant information sheet will be emailed/posted to the participant alongside confirmation of their screening/baseline appointment. The researcher will explain the participants are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason. No research procedures will be conducted prior to taking consent from the participant. Consent will not denote enrolment into the trial.

A copy of the signed Informed consent form will be given to the participant. The original signed form will be retained at the study site and a copy placed in the medical notes.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and participants will be re-consented as appropriate.

10.3 SCREENING PERIOD

As previously outlined in section 9.2 (Recruitment) and 11.1 (Patient Identification), once consent to contact has been established, patients will be assigned a screening ID and contacted by a member of the research team to arrange a telephone call where they will go through the telephone screening questionnaire.

Telephone screening questionnaire: The screening questionnaire was developed by the research team to understand the patient's eligibility for the trial. The questionnaire asks about previous contact with healthcare services, evidence of tics, previous and current interventions for tics and other disorders, other diagnoses/problems, type of education facility attended, access to the internet, age of child and other basic eligibility criteria. As part of this any potential barriers to participation in the intervention will be looked at. The questionnaire is designed to determine eligibility to attend the baseline face-to-face appointment. The questionnaire takes approximately 20-30 minutes to complete.

Patients who meet the eligibility requirements discussed over the telephone appointment will be invited to attend a screening/baseline appointment. The appointment will be held at one of the two study sites (GOSH/NHCFT). All patients will be reimbursed for their travel costs to attend this appointment. There is no specified deadline from receiving initial consent to contact to participants undergoing their screening appointment. We anticipate most screening appointments being conducted within 1-month of receiving consent to contact. However, if the trial therapist's caseload is full they may be delayed. If this occurs, the research team will update the patient every month with a letter informing them of the progress and likely time frame to be contacted.

Before participants attend the screening/baseline appointment parents will be asked to complete an online DAWBA.

Development and Wellbeing Assessment (DAWBA) (Goodman et al., 2000): The DAWBA is a package of interviews and questionnaires completed by parents and teachers and designed to generate ICD-10 and DSM-IV / DSM-5 psychiatric diagnoses for children and young people. The DAWBA computer algorithm estimates the probability of having a psychiatric disorders in bands of <.1%, .5%, 3%, 15%, 50% and > 70% based on large community-based population studies (Goodman et al., 2000), the top two levels have been shown to reliably indicate presence of a clinician-rated diagnosis and can be used as an alternative to clinician-rated diagnoses in research studies (Goodman et al., 2011). The DAWBA has established validity and reliability (Goodman et al., 2000) and will be completed online, via the DAWBA platform, prior to baseline appointment to ascertain patient eligibility. The parent DAWBA can take between 20 minutes to 2 hours to complete dependent on the complexity of symptoms; the teacher version takes less than 30 minutes. Both parent and teacher DAWBAs start with an SDQ. If the participant is later enrolled in the trial, this will be used as their baseline SDQ. Completion of the parent DAWBA is a requirement for enrolment into the trial, findings from the DAWBA will be

used to exclude people who are rated as being likely (50-70%) to have, self-harm, psychosis and anorexia nervosa or suicidality. DAWBAs that score people as being likely to have these conditions will be second reviewed by the CI (and medical expert) to ascertain that they should definitely be excluded from the trial. If the DAWBA indicates high likelihood of suicidality the participants GP or usual treating clinician will be informed.

The study team will provide log-in details to enable the participants to complete the DAWBA. Parents will also be given log-in details for the child's teacher to log-in and complete the teacher-rated DAWBA. It is up to the parent if they wish to involve the teacher in this process and it is their decision to give the DAWBA details to the teacher. The parents will be encouraged by the research team to involve the teacher if possible as this results in more reliable DAWBA diagnostic predictions. Participants may enter the trial without a teacher completed DAWBA but must have a parent completed DAWBA prior to enrollment. Potential participants who meet the initial eligibility criteria will be emailed/posted the participant information sheets about the study alongside a confirmation of the time/location of their screening/baseline appointment.

At the screening/baseline appointment, the researcher will further discuss the study requirements with the patient, explain the research process, provide an opportunity to ask questions about the research or the intervention and take fully informed consent from the parent/carer and child/young person (see section 11.2 'Informed Consent Procedure'). The researcher will go through the eligibility criteria discussed over the telephone and conduct the YGTSS assessment and the CAIDS-Q. Details of the YGTSS can be found under Section 8.1 'Primary Outcome'. Details of the CAIDS-Q are listed below.

Child and Adolescent Intellectual Disability Screening Questionnaire (CAIDS-Q)(McKenzie et al., 2013): The CAIDS-Q is being utilised to determine the presence of intellectual disability at baseline. The questionnaire contains seven-items (two on literacy, one on telling the time, one on friendships, two on previous contact with specialist services and current educational support and one on tying laces. They are answered in a Yes/No format by someone who knows the person well and some items can be tested directly with the child (depending on age/communication). The items have been used successfully in an online format in various studies. A total score is calculated which is converted to a percentage score. A cut-off (by age group) indicates if the child is likely to have an intellectual disability or not. The score can also be used as a proxy for IQ in situations where only an approximate indication of intellectual ability is needed and will be used in this study to exclude participants who are likely to have an intellectual disability. The questionnaire has established validity and reliability (McKenzie et al., 2013). The questionnaire will be completed by the assessor with the family at the screening/baseline assessment and takes less than 5 minutes to complete.

If through the process of determining eligibility, the assessor is concerned that the potential participant may require immediate access to highly specialised services, they will ask the CI to review these cases before enrolment into the trial.

Methods for ensuring satisfactory completion of the eligibility criteria have been described under Section 10.1 'Inclusion Criteria'.

Patients who fail screening because they have recently changed (started or stopped) their tic medication (within 2-months), or received a behavioural therapy within the specified exclusion time frame (12 months), may be eligible for re-screening at a later date when these time exclusions have passed.

Patients who meet the eligibility criteria, after completion of all screening assessments, will be asked to complete baseline measures. After completion of baseline measures, patients will be randomised into the study by the researcher via the web-based system hosted on a secure server by Sealed Envelope. This will happen at or just after the screening/baseline appointment (prior to starting to the treatment). At the point of randomisation, patients will be enrolled into the trial and be given a study ID.

At the screening/baseline appointment participants will be introduced to the BIP system and provided with log-in details by the assessor, where possible, they will also be briefly introduced to their therapist who will provide the online support throughout the trial. At this appointment the assessor and participant will agree a start date for commencing therapy with their assessor (typically within 24-48 hours of the baseline appointment, with a maximum of 7-days after baseline appointment). The participant will be reminded that it is important that they log-on and start the therapy as close to the allocated start date as possible. After the participant is randomised, an email notification will be sent to specified members of the research team. For assessors and the trial manager, this notification will simply contain the participants study ID without arm allocation, for unblinded administrators and therapists this will email will contain notification of arm allocation. Either the therapist or an unblinded administrator will add the parent/carer and child/young person to the correct treatment allocation in the BIP system. This arm allocation will be double checked by either the therapist or the administrator before commencing treatment.

10.4 RANDOMISATION PROCEDURES

Participants will be randomised online by the researcher/assessor conducting screening/ baseline. Randomisations will distributed equally between the two arms (ratio 1:1), and stratified by group location (London or Nottingham) using block randomisation with varying block sizes. The researcher will remain blind to the

treatment allocation, and the therapist will be notified of the treatment allocation. Therapists will set-up participants' treatment on the BiP system.

10.5 UNBLINDING

Randomisation will be conducted using Sealed Envelope online randomisation system. The online randomisation system is managed by Priment CTU (UCL). The randomisation system will ensure that researchers/outcome assessors remains blind to intervention allocation notifications. All participants receive the same outcome measures so assessors will not know which group the participant is in by the measurements. Participants will be reminded by their assessor at the beginning of each follow-up assessment that they are not to disclose arm allocation to them. If an assessor becomes unblinded, subsequent assessments for that participant will be conducted by a different assessor (blind to arm allocation) where possible.

In case of a medical emergency, participants will be able to disclose to the treating physician (e.g. GP) what treatment they received without unblinding the researchers. As such, an emergency unblinding system is not required for this study. Additionally, the participants will be having regular contact with therapist during the 10-week intervention who can provide further details on the intervention to a HCP if required.

10.6 BASELINE ASSESSMENTS

The following measures will be collected from participants at baseline:

1. *Demographics questionnaire*: To understand the characteristics of the sample the research team have created a demographics questionnaire which asks for the child's age, gender, ethnicity, parental education/ occupation, list of the child's current diagnoses and interventions (including medications) and GP and school details. The questionnaire is designed to be completed by the researcher as part of the baseline assessment with the parent/carer. The questionnaire takes less than 10 minutes to complete.
2. *Social Communication Questionnaire (SCQ)*(Rutter et al., 2003): The SCQ is a screening tool for Autism Spectrum Disorder (ASD). The tool was developed as a screening instrument to identify children who already have some indication of a developmental issue and should undergo additional assessment for ASD. The SCQ consists of 40 items and is a parent-report questionnaire asking about characteristic autistic behaviour at the age of 4 to 5 years and currently. Total scores can range from 0 to 39. The authors recommend a cut-point for differentiating between likely ASD and non-ASD diagnoses of 15 based on the total SCQ score (sensitivity = 0.85, specificity = 0.75). The questionnaire has established validity and reliability (Chandler et al., 2007). The SCQ will be completed by the

parent/carer at baseline via the BASS platform (online) with the aim of describing the characteristics of the sample. The questionnaire takes approximately 10 minutes to complete.

3. *Premonitory Urge for Tics Scale (PUTS)* (Woods et al., 2005): The PUTS is a self-report instrument specifically designed to measure the current frequency of different types of PUs in patients with tic disorders. Examples are "Right before I do a tic, I feel like my insides are itchy" (Item 1) and "Right before I do a tic, I feel like there is energy in my body that needs to get out" (Item 6). The original version of the PUTS has 10 questions scored 1–4 (not at all – very much), with higher values representing a greater frequency of premonitory urges. The PUTS total score ranges from 9-36, with items 1-9 counting towards the total score. The questionnaire has established validity and reliability (Woods et al., 2005). The PUTS will be completed by the child/young person at baseline via the BASS platform. Where needed, the parent/carer can support the child/young person in completing the measure. The questionnaire will take approximately 5-10 minutes to complete.
4. *Swanson, Nolan, and Pelham Rating Scale (SNAP-IV)* (Swanson et al., 2001): The SNAP-IV is a behavioural rating scale that employs the core symptoms of ADHD and oppositional defiance disorder (ODD) as defined by the Diagnostic and Statistical Manual of Mental Disorders. The SNAP-IV consists of 26-items that are rated on a 4-point scale (not at all, just a little, quite a bit, very much). The items are divided between three sub-scales which can be used to create scores for: inattention (9-items), hyperactivity/impulsivity (9-items), oppositional (8-items). Items for inattention and hyperactivity/impulsivity can be combined to also create a 'combined ADHD' score (Bussing et al., 2008). Sub-scale scores are calculated by summing items on that subset and dividing by the number of items in the subset (creating an average). Scores above the 95th percentiles are considered clinically relevant. The questionnaire has established validity and reliability (Bussing et al., 2008). The SNAP-IV is completed by the parent/carer at baseline via the BASS platform (online) to define the sample characteristics. The questionnaire takes less than 5 minutes to complete.
5. Child & Adolescent Gilles de la Tourette syndrome Quality of Life (C&A-GTS-QOL) – see Section 8.2 'Secondary Outcomes'.
6. *Parent Tic Questionnaire (PTQ)* – see Section 8.2 'Secondary Outcomes'.
7. *Children's Global Assessment Scale (CGAS)* – see Section 8.2 'Secondary Outcomes'.
8. *Child Health Utility 9D (CHU9D)* – see Section 8.2 'Secondary Outcomes'.
9. *Modified Client Service Receipt Inventory (CSRI) (including a measure of school attendance)* – see Section 8.2 'Secondary Outcomes'.
10. *Moods and Feelings Questionnaire (MFQ)* – see Section 8.2 'Secondary Outcomes'.
11. *Spence Child Anxiety Scale (SCAS)* – see Section 8.2 'Secondary Outcomes'.
12. *Adverse events/side effects* – see Section 8.2 'Secondary Outcomes'.

The scores from the YGTSS (Severity scale and impairment scale) collected as part of screening at the screening/baseline appointment will be used as the baseline YGTSS (severity and impairment scores). The SDQ collected as part of the DAWBA will be used as the baseline SDQ.

Table 1 outlines the completion time points for each measure and who completes them under section 11.9 'Flowchart of Study Assessments'.

The majority of the measures will be completed online via the BASS system. At baseline, the researcher will set the participants up on the BASS platform so they can complete baseline measures, this will involve providing log-in details. Families who log on to the BiP platform to complete the intervention can be directly transferred to the BASS platform to answer the child- and parent rated questionnaires. The data are then directly saved in the BASS platform for later extraction. After completion of measures in BASS participants are provided with an automated message which suggests avenues to seek medical help if the questionnaires have raised any significant concerns about their child's health.

Assessor/researcher completed measures are also inserted into an online platform (but may be completed on paper first). Families are reminded about measure completion via automatic reminders sent in BASS, or email or SMS, where they are sent a link directing them to the BASS platform. If measures are not completed further email or SMS reminders can be sent via the BASS system from the research team. Participants login with their login details provided at the screening/baseline appointment and are then sent an SMS message directly to their phone that contains a verification code which is needed to enter the BASS platform. The exceptions to this are the YGTSS which is completed face-to-face at baseline and the DAWBA which is completed online via the DAWBA website. All YGTSS baseline assessments will be video-recorded for spot methodology checks if needed or if a new assessor is recruited. The videos will only be seen by approved members of the research team. Participants are made aware of this in the participant information sheet. The screening questionnaire is completed by the researcher over the telephone and then subsequently entered into BASS, as is the demographic questionnaire completed by the researcher (with the family) at the baseline assessment. The CAIDS-Q, CSRI and demographics questionnaire will also be conducted by the researcher/assessor with the parent/carer and later entered into the BASS system. This is to ensure that the researcher/assessor can determine eligibility before the participant proceeds to completing other baseline measures and to help them complete the CSRI which is best done with researcher support.

Participants will be expected to complete all baseline measures at the baseline assessment (prior to randomisation). The only exception is for teacher completed DAWBA which is not required to determine eligibility, thus this may be completed up to 3-months post enrollment in the trial.

Participants will be reimbursed with £20 voucher for completion of baseline measures.

10.7 TREATMENT PROCEDURES

BiP is a Swedish web-based platform that has been specifically designed for use by children and young people and their parents, with age-appropriate appearance, animations and interactive scripts (http://www.bup.se/BiP/).

There are 10 chapters for each intervention, each designed to last 10 weeks. Patients have regular contact with an experienced, trained therapist during this time via messages that can be sent inside the treatment platform (resembling an email). The therapist can directly comment on exercises that the patient has been working on, and give specific feedback to motivate the patient. The patient typically has contact with the therapist several times a week.

If necessary, it is possible to allow the therapist guided treatment to be given over a 12 week period, as long as the therapist only offers support for a maximum of 10 weeks during the 12 week period. This may be needed if the participant is unable to engage with the ORBIT treatment for a period of time for reasons such as, holidays, exam periods, illness or bereavement.

If any circumstance occurs meaning the child is unable to login and access the ORBIT treatment for 5 days or more, therapist support and access to BiP TIC should be paused for that week, until the child is able to fully engage in the treatment again. Treatment and therapist support can be paused for a maximum of two weeks. Therapists will consult with the trial manager and their clinical supervisor for these cases.

For the tic-focused intervention 'BiP Tic', the treatment manual (constructed by the co-applicants) consists of evidence-based interventions adapted from previously published treatment manuals on Exposure and Response Prevention (ERP) and established behavioural intervention for tics protocols (Piacentini et al., 2010, Woods et al., 2008, Verdellen et al., 2011b) . Each of the 10 modules includes age-appropriate texts, animations and exercises. The first four modules cover the main content of the treatment; completion of these four child modules is a minimum requirement to meet treatment completion criteria. The intervention is based on ERP techniques. During the treatment, participants are instructed to practice suppressing their tics, this is known as 'response prevention'. Then, with the help of their parent/carer, the participant is instructed to provoke premonitory urges (the urge to tic often felt before the tic is expressed) and try to supress the need to express/demonstrate the tic, this known as 'exposure'. The breakdown for the module content is as follows:

1. *Child*: Learn about tics. *Parent*: Introduction
2. *Child*: More about tics. *Parent*: Supporters thoughts and behaviours

3. *Child*: Practicing stopping your tics. *Parent*: Praise
4. *Child*: Making the practice more difficult. *Parent*: Prompts
5. *Child*: Continued practice. *Parent*: Situations and reactions
6. *Child*: School. *Parent*: Trouble shooting
7. *Child*: Talking about your tics. *Parent*: Continued practice
8. *Child*: Continued practice. *Parent*: Continued practice
9. *Child*: The final spurt. *Parent*: Continued practice
10. *Child*: Plan for the future. *Parent*: Plan for the future

The child/young person and the parent/carer are provided with their own separate login to the BiP platform. The parent login allows them to access information regarding parent coping strategies, social support and functional analysis relating to tics. Both parents/carers and children/young people have the same access to the therapist.

During the screening/baseline assessment (prior to starting the therapy), participants are introduced to the BiP platform, and where possible meet their therapist. During the treatment, the participants receive remote contact with this therapist via an inbuilt text message function in the system (similar to an email), at the same time they also get an SMS reminder delivered to their phone through the BiP system each time they have received a new message from their therapist inside the BiP platform. Phone calls to the family may also be made when the participant/therapists feels it is necessary. Therapists login to the system to provide the participants with feedback, answer questions or remind them to complete the next chapter/module if required. The amount of contact the therapist has with the family is determined on an individual basis as the therapist deems necessary. Results from the pilot study suggest that on average the therapist has approximately 24 minutes of contact each week with the family. Any phone calls made outside the BiP system are not logged in the BiP system, but recorded manually in a data file. All therapist activity is logged in the system. Additionally, therapists keep their own log of contacts in an Excel file. This file allows them to keep track of when a chapter/module was opened to check progress, and also provide a brief log of messages/contacts with the family. The therapist should login at least every 48 hours of a working week, but are advised to log in daily to check for messages/inactivity.

The therapist is only available to support the participants during the 10-week intervention window (or a maximum of 10weeks delivered over a 12-week period). Access to the BiP system is granted for 1-year, however, after the 10-weeks of therapist support, this access is without therapist support. Regardless of how far through the chapters the participant got within the 10-week supported intervention, all the chapters are open to the family for the 1-year period.

A parallel comparator intervention consisting of psychoeducational information about TS and co-occurring conditions has been developed. This intervention is also delivered via the BiP platform and follows the same procedure as the behavioural therapy intervention, as

such, the comparator intervention also consists of 10-chapters that have been designed to be delivered over 10-weeks, with therapist support through the BiP system. The chapters have been matched in length to that of the behavioural intervention, the main difference is the content.

The comparator intervention will review the definition of tics, natural history, common presentations, prevalence, aetiology, risks and protective factors and strategies for describing tics to other people etc. Problem-solving and development of expertise in tic disorders is emphasised. The intervention will include strategies for promoting positive behaviours which will be rewarded by a parent as a parallel element to the tic control practice in the behavioural therapy arm. There will be no information on tic control within the management package. Parallel programmes will be offered to children and parents. The material has been adapted and updated from the psychoeducational intervention used in the large, multi-centre trial CBIT trial (Piacentini et al., 2010). The content of the chapters is as follows:

1. *Child*: Introduction *Parent*: Introduction
2. *Child*: Tics and Tic list *Parent*: Thoughts and behaviours of supporters
3. *Child*: Learning about tics. *Parent*: Praise
4. *Child*: More than tics. *Parent*: More than tics
5. *Child*: Tics and the future *Parent*: Prompts
6. *Child*: School. *Parent*: School
7. *Child*: More expertise on tics. *Parent*: Looking after yourself
8. *Child*: Risk and protective factors. *Parent*: Supporting your child: Risk and protective factors
9. *Child*: Healthy Habits. *Parent*: Healthy habits for your child
10. *Child*: Plan for the Future. *Parent*: Plan for the Future and FAQs

For both the intervention and the comparator, treatment completion is defined as completion of the first four child chapters.

The participant will agree a start date for commencing therapy with their assessor at the screening/baseline appointment (typically within 24-48 hours of the baseline appointment). The participant will be reminded that it is important that they log-on and start the therapy as close to the allocated start date as possible. Regardless of which treatment arm the participant is in, at this point the therapist will release the first two chapters of the intervention for the participants to complete and monitor their progress, sending reminders and feedback where necessary to ensure the family progress through the chapters in a timely manner. If the participant does not start the intervention at the agreed start time, the 10-week start date does not alter. However, as previously mentioned, the 10-weeks of therapist support may be delivered over 12-weeks, but the total therapist contact will not exceed 10-weeks.

10.8 SUBSEQUENT ASSESSMENTS

The following data are collected at follow-up:

Treatment Credibility: (3 weeks post randomisation)

1. Treatment credibility (outcome variable). There is a +14 days' time period for data collection.

Follow-up 1: Mid-treatment (5 weeks post randomisation)

1. Parent Tic Questionnaire (PTQ)
2. Moods and Feelings Questionnaire (MFQ)
3. Adverse events/side effects

This follow-up occurs 5-weeks into the treatment period. For measures collected at this time point there is a +14 days' time period for data collection.

Follow-up 2: Post treatment – (3 months post randomisation)

1. Parent Tic Questionnaire (PTQ)
2. Yale Global Tic Severity Scale (YGTSS) (severity and impairment scale)
3. Children's Global Assessment Scale (CGAS)
4. Clinical Global Impressions (CGI) – improvement
5. Strengths and Difficulties Questionnaire (SDQ)
6. Child Health Utility 9D (CHU9D)
7. The Child and Adolescent Version of the Gilles de la Tourette Syndrome Quality of Life Scale (C&A-GTS-QOL)
8. Modified Client Service Receipt Inventory (CSRI) (including school attendance)
9. Moods and Feelings Questionnaire (MFQ)
10. Spence Child Anxiety Scale (SCAS)
11. Adverse events/side effects
12. Treatment satisfaction
13. Need for further treatment
14. Concomitant interventions
15. A sub-sample of participants will also be invited to interview (Telephone or face to face, including WebEx as dictated by patient preference or feasibility) as part of the Process Evaluation.

This follow-up occurs 2-weeks after the intervention is complete. For this follow-up there is a -2 weeks/+2 month time period for data collection.

Follow-up 3. 4 & 5: (6, 12 and 18 months post randomisation)

1. Parent Tic Questionnaire (PTQ)
2. Yale Global Tic Severity Scale (YGTSS) (severity and impairment scale)
3. Children's Global Assessment Scale (CGAS)
4. Clinical Global Impressions (CGI) – improvement
5. Strengths and Difficulties Questionnaire (SDQ)
6. Child Health Utility 9D (CHU9D)
7. The Child and Adolescent Version of the Gilles de la Tourette Syndrome Quality of Life Scale (C&A-GTS-QOL)Modified Client Service Receipt Inventory (CSRI) (including school attendance)
8. Moods and Feelings Questionnaire (MFQ)
9. Spence Child Anxiety Scale (SCAS)
10. Concomitant interventions
11. Adverse events/side effects (collected at follow-up 3 (6 months) only)

For these follow-ups there is a -1 month/+2 month time period for data collection.

With the exception of the measures completed by the assessor/researcher, all follow-up completed measures will be completed via the BASS platform (described above in baseline assessments). Measures completed by the assessor/researcher will be completed on paper CRFs and then entered into BASS. The YGTSS will be completed at follow-up via a video-conference facility, WebEx. WebEx does not involve the participant downloading any software, instead they are emailed a link by the research team and click on the link to initiate the video conference. WebEx is outlined to participants in the participant information sheets. WebEx is a global enterprise-scale network designed specifically for highly secure delivery, including consistent availability and multilayer tenant security validated by vigorous independent audits, including SSAE-16 and ISO 27001. WebEx is certified by the Skyhigh Cloud Trust Programme, the most extensive and impartial evaluation of cloud security available. WebEx has been used in previous RCTs looking at online delivery of therapy (e.g. "Helping Urgent Care Users Cope with Distress about Physical Complaints: A Randomised Controlled Trial" REC Reference 14/LO/1102). If the WebEx service fails or participants explicitly request not to use videoconferencing facilities, the YGTSS will take place over the telephone. For accurate YGTSS scores the assessor should be able to see the participant during the assessment, however, a telephone appointment would be preferable to missing data, although may reduce the quality of the data. The YGTSS conducted over WebEx may be recorded. Participants are made aware of this in the participant information sheets, and the assessor will confirm consent before starting each recording. The method of completion for YGTSS will be recorded.

Participants will be given £20 worth of vouchers for completing measures at baseline each follow-up time point, except the mid-treatment follow-ups (3 and 5 weeks).

10.9 FLOWCHART OF STUDY ASSESSMENTS

As this is an online study there are no scheduled visits (with the exception of the baseline appointment). The baseline measures are conducted at the screening/baseline appointment either with the researcher or via the BASS platform. All follow-up measures are completed online via the BASS platform or over WebEx/video-conferencing or telephone at follow-up.

Table 1. Baseline and outcome measures

Months post-randomisation	**0**	**0**	**1**	**1**	**3**	**6**	**12**	**18**	**Completed by**
Time Point	Telephone screen	Baseline	Mid-treatment (3wk)	Mid-treatment (5wk)	Primary End point	6-months	12 months	18-months	
Consent		X							P/C
Randomisation		X							R
PTQ		X		X	X	X	X	X	P
CAIDS-Q		X							P/R
SCQ		X							P
Screening for eligibility	X	X							R
SDQ &DAWBA (conducted post telephone screen & prior to baseline)	X								P & T
YGTSS (0-50) Total Tic Severity Score		X			X	X	X	X	R
PUTS		X							C
CGI Improvement (CGI-I)					X	X	X	X	R
CGAS		X			X	X	X	X	R
YGTSS Impairment		X			X	X	X	X	R

Months post-randomisation	**0**	**0**	**1**	**1**	**3**	**6**	**12**	**18**	**Completed by**
Time Point	Telephone screen	Baseline	Mid-treatment (3wk)	Mid-treatment (5wk)	Primary End point	6-months	12 months	18-months	
SDQ (P)					X	X	X	X	P
CHU9D		X			X	X	X	X	P/C
Modified CSRI (inc school attendance)		X			X	X	X	X	P/R
MFQ-(Self-report)		X		X	X	X	X	X	C
SCAS (Self-report)		X			X	X	X	X	C
C&A GTS-QOL		X			X	X	X	X	C
SNAP-IV		X							P
Demographics		X							R
Adverse effects/side effects		X		X	X	X			P/C
Treatment credibility			X						P/C
Treatment satisfaction					X				P/C
Need for further treatment					X				P/C
Interview (Process Evaluation)					X				
Concomitant interventions		X			X	X	X	X	P/R

Key: P = parent; C = child; R = researcher; T = teacher; PUTS = Premonitory Urges for Tics Scale; PTQ = Parent Tic Questionnaire; SCQ = Social Communication Questionnaire; YGTSS = Yale Global Tic Severity Scale; C&A-GTS-QOL = The child and adolescent version of the Gilles de la Tourette Syndrome Quality of Life Scale; CGAS = Children's Global Assessment Scale; CGI-I = Clinical Global Impressions; SDQ = Strengths and Difficulties Questionnaire; DAWBA = Development and Wellbeing Assessment; CHU9D = Child Health Utility 9D; CSRI = Client Service Receipt Inventory; MFQ = Moods and Feelings Questionnaire; SCAS = Spence Child Anxiety Scale.

10.10 METHODS

10.10.1 LABORATORY PROCEDURES

There are no laboratory procedures for this study.

10.11 DEFINITION OF END OF TRIAL

The end of the trial will be the date of the last visit/ telephone follow up/ WebEx by the last participant.

10.12 DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS AND 'STOPPING RULES'

Data on the impact of the intervention on reducing tics and other outcome measures will not be analysed until the end of the study period and therefore will not inform decisions to stop the research. However, SUSARs and serious adverse reactions will be reviewed and if there is any indication that these are linked to the intervention consideration will be given to stopping on the advice of the Trial Steering Committee (TSC) and Data Safety and Monitoring Board (DSMB) and study Sponsor.

Another reason for stopping the trial prematurely would be poor recruitment and engagement with the treatment intervention which does not improve despite attempts to engage healthcare professionals and service users. This will be reviewed after the 9-month internal pilot. If the targets for recruitment or engagement are not met, the trial may be terminated on advice of the TSC, DSMB and the study funder.

The objective of the internal pilot is to determine whether recruitment, engagement with the intervention and retention to the trial are sufficient to allow the trial to progress and provide a definitive answer on the effectiveness of the intervention. The internal pilot runs for the first 9-months of recruitment. Allowing for a staggered start to recruitment, the stop/go rules for the internal pilot are as follows:

1) The study needs to have recruited 66 patients by the end of the 9th month of recruitment
2) At least 60% of participants need to have completed the intervention (with completion defined as completing at least the first 4 child chapters).
3) 80% of participants who have reached the relevant time window need to have completed the primary outcome measure (YGTSS) at the primary end point (3-months), within the specified time frame for measure completion.

If these criteria are not met the trial may be terminated. This decision will be made by the TSC.

Participants are free to withdraw from the trial at any point. If participants indicate to the research team/therapist that they would like to withdraw from the study, they will be sent a 'confirmation of withdrawal' letter by the research team. Participants will be made aware in the participant information sheets that any non-identifiable data collected up to the point of withdrawal may still be used in the study analysis. After confirmation of withdrawal has been confirmed, participants will not be requested to complete any further measures but will be asked by the research team to provide non-obligatory feedback to the research team as to why they withdrew. This will help inform the future development of trials and the

intervention. The reason will be recorded in a log of withdrawals, on their CRF and on the trial master file database. Once participants have withdrawn from the study it will not be possible to re-enter the study or resume treatment. Withdrawn participants will not be replaced into the study.

Participants will not be withdrawn from the study if they are not active in treatment. If the child is inactive and has stated they do not wish to continue to be part of the treatment the therapists will encourage the parent to login and continue with the parent chapters of the treatment. Treatment completion will be taken as completion of at least the first 4 child chapters. However, only in cases where the participants (both parent and child) clearly state they do not wish to part of the trial anymore, or complete any more follow-up measures, will they be withdrawn from the trial. If participants do not wish to continue with the therapy, we would still invite them to complete outcome measures unless they explicitly state otherwise. In this case participants will be informed it is still helpful to the study team to collect outcome measures, even if they don't want to be part of treatment.

Failure to complete outcome measures at one follow-up time point will not imply withdrawal from the study, and the participants will still be invited to complete measures at the next follow-up time point, unless they explicitly state otherwise.

10.13 CONCOMITANT MEDICATION

Participants will not be asked to stop/ withdraw from medication for tics as part of the trial. This information will be recorded on 'concomitant treatment'. It is likely that a significant proportion of the young people in the study will be on medication for tics or for other mental health conditions (such as ADHD). This is prescribed and monitored by their usual treating clinician within their Trust. There are no exclusion criteria related to specific drugs, however, participants must not have started or stopped medication for tics within the 2-months prior to joining the trial. For any issues regarding any prescribed medication, participants will be informed to seek advice from their usual treating clinician.

Participants must not have received a previous structured behavioural intervention for tics (CBIT/ERP/HRT) in the 12-months leading up to their commencement into the trial. They should not start any new structured behavioural interventions for tics outside the trial intervention during the first six months of the trial, similarly, clinicians are asked not to start/stop their medication for tics if possible during the first six months of the trial. However, if medication/therapy needs to be changed as a result of side-effects or adverse events this may happen and the participant will still be included in the intention-to-treat analysis. A note of this will be made and considered as part of the statistical analysis. Participants may receive ongoing or new therapy/medication as part of their intervention for other concomitant diagnoses throughout the study.

After six-months, participants enter the 'naturalistic follow-up' and may freely change/start medication or therapy for their tics or other disorders. Use of other therapies/medication is recorded at each follow-up time point.

10.14 POST-TRIAL ARRANGEMENTS

Participants will still be able to access the chapters hosted on the BiP platform post 10-week intervention. They will be able to log in to the BiP system and refer to these chapters for self-guidance 1-year after starting the treatment, but will no longer receive therapist support provided through the 10-week intervention period (which may be delivered over 12-weeks). If participants would like to discuss any issues relating to their tics outside of the trial period they will be informed on the participant information sheets they should seek contact with their usual treating clinician.

11 DATA MANAGEMENT

All aspects of data management of the study will comply with the UK Data Protection Act 1998, Priment SOPs and GCP.

Information about the trial in the participant's medical records/ hospital notes will be treated confidentially in the same way as all other confidential medical information.

11.1 CONFIDENTIALITY

The Case Report Forms (CRFs) will not bear the participant's name. The participant's initials, date of birth and trial identification number will be used for identification. Any personal data collected will be managed according to Priment SOP Managing Personal Data.

11.2 DATA COLLECTION TOOLS

The data collection tools will be created according to Priment SOP Development, Review and Approval of Case Report Forms. The CRF will only collect the minimum required information for the purposes of the trial. CRFs and video recordings will be held securely in a locked room or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities.

11.3 TRIAL DATABASE

The CRFs will be entered into a web-based clinical data management system, Red Pill, provided by Sealed Envelope and set up by Priment CTU. Sealed Envelope has been assessed by Priment to ensure that adequate processes are in place and are being followed for quality management, software development and security. Database services and support will be delivered through a contract signed by Sealed Envelope and UCL.

Priment SOPs Validating Sealed Envelope Systems and Change Control for Sealed Envelope Systems will be followed to set up and manage changes to the trial database.

At the end of the trial, prior to analysis, Priment SOP Database Lock, Unlock and Closure will be followed.

Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method). Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

11.4 DATA COLLECTION AND HANDLING

All data will be collected and handled in accordance with Priment SOP Data Handling.

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

Data collection/handling/storage of BASS, BiP and DAWBA:

Data will be collected both manually (paper CRFs) and digitally (in BASS rating platform and DAWBA).

The DAWBA is a well-established research tool which has been used extensively in clinical trials (e.g. “Assessing QbTest Utility in ADHD, REC Reference 14/WM/0166). To maximise confidentiality and keep potentially sensitive information safe from hackers, the DAWBA online system doesn't know the identity of the people being assessed - only the clinic or research group knows which person has which ID. Additional security is provided by using a secure server with encryption.

BiP is the platform that delivers the therapy. BiP may contain personal sensitive information such as conversations between the therapist and YP. Whenever administrative personnel or assessors/therapists edit patient data, this action is logged. The log is saved until it is manually cleared. To ensure privacy, assessors/therapists can only access their own participants. BiP has a fine-grained privilege-system which ensures that administrators and assessors/therapists can only view information and edit settings that pertain to their role in a research project. All data sent between the BiP platform and the user are encrypted using a 2048-bit SSL certificate. The system is setup so that only a port 80 and 443 is visible on the internet to the public. A firewall called ModSecurity is also installed on the server where different rules can be activated. The server has rules activated to prevent attacks with SQL injection and brute force. The server will also be continuously updated by the server-

company (GleSYS) that installs security-patches when they are released, as another measure to prevent hackers (or similar).

The BASS is a rating platform stored on a Swedish server. BASS is used to collect all outcome measures, including personal sensitive information. At baseline, the researcher will set the participants up on the BASS platform so they can complete baseline measures. Families who log on to the BiP platform to complete the intervention can be directly transferred to the BASS platform to answer the child- and parent rated questionnaires. The data are then directly saved in the BASS platform for later extraction. Researcher completed measures are also completed in the BASS platform. Whenever administrative personnel or assessors/therapists view or edit patient data, this action is logged. To ensure privacy, assessors/therapists can only access their own participants. BASS also has a fine-grained privilege-system which ensures that administrators and assessors/therapists only can view information and edit settings that pertain to their role in a research project. All data sent between the platforms and the user are encrypted using a 2048-bit SSL certificate. The system is setup so that only a port 80 and 443 is visible on the internet to the public.

Both the BiP and BASS system will store names of participants and details for SMS reminders. Date of birth is not stored in either BiP or BASS. This sensitive information will only be stored in the trial coordinator document, accessed by the Trial Manager and held on a password protected, secure computer at the University of Nottingham. Once the study is finished, all personal information (names etc.) are removed from the BiP and BASS systems. Logging into the BiP and BASS platform requires both username and password plus a temporary code sent by SMS (i.e., two-factor authentication which is required for systems storing sensitive data).

Data extraction will be completed from the UK, by logging in to the Swedish server and downloading data into Microsoft Excel format. Data can be accessed by the BASS administrator Per Andrén (Karolinska Institutet, Sweden), the trial manager and researchers. Group allocation is visible in the BiP system for the therapist of each participant and is stored in a separate document (administered by an independent member of the team) and later added as a variable to the extracted Excel document from the BASS platform.

Data from Sealed Envelope will be downloaded by trial statistician, and data from BASS will be downloaded as a csv file for analysis. Only non-identifiable data will be sent to the CTU by the research team. Transfer will be via secure (university or NHS) email address. The data will be encrypted and password protected before it is transferred.

Messages to and from the family will be in the form of the templates provided in the application. These will be treated in the same manner as all confidential data and will be kept for up to 12-months after the end of the trial, this is outlined in the PIS. Messages sent in BiP may be analysed as part of the Process Evaluation and as such will be treated in the same way as other outcome data (stored for 5-years after trail completion).

Video files and audio transcriptions

The audio and video recordings will be stored on a secure, encrypted external hard drive which is recommended by the lead Trust and Sponsor (Nottinghamshire Healthcare NHS Foundation Trust). The hard drive will be stored in a secure, locked cupboard with restricted access to only approved members of the research team. The hard drive will also be used to transfer the video/audio data between the sites. Video and audio recordings will be treated as research data and thus kept for 5-years in accordance with the Sponsor policies. The videos will only be used to conduct quality checks of inter-rater reliability and will only be viewed for this purpose by approved members of the research team.

The audio recordings will be conducted by an external organisation approved by the Sponsor. Any recording sent to and from the external organisation will be sent encrypted and password protected.

The transcripts (which have been edited to remove identifiable information at the point of transcription) will be stored with the assessment and outcome data (secure, locked cupboard with restricted access or secure computer described on page 53) and will only be accessible by approved members of the research team.

11.5 DATA OWNERSHIP

At the end of the trial, the data belongs to Professor Chris Hollis (CI) and Nottinghamshire Healthcare NHS Foundation Trust (study sponsor).

12 RECORD KEEPING AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with Nottinghamshire Healthcare NHS Foundation Trust Research Code of Conduct and Research Ethics, the Chief Investigators will be responsible for the secure archiving of essential trial documents (for each site, if multi-site trial) and the trial database as per their trust policy. All essential documents will be archived for a minimum of 5 years after completion of trial. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility. Personal data, such as contact details, will be destroyed after it is no longer necessary to contact a participant.

The Trial Master File, trial documents and trial database held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at Nottinghamshire Healthcare NHS Foundation Trust. This archive shall include all trial databases and associated meta-data encryption codes. Destruction of essential documents will require authorisation from the Sponsor. Archiving will be authorised by the Sponsor following submission of the end of study report.

13 STATISTICAL CONSIDERATIONS

Louise Marston is the lead statistician who will be responsible for all statistical aspects of the trial from design through to analysis and dissemination. Duties will be delegated to the trial statistician, Rebecca Jones. A more detailed statistical analysis plan will be produced prior to analysis by randomised group.

13.1 STATISTICAL ANALYSES

13.1.1 SUMMARY OF BASELINE DATA AND FLOW OF PARTICIPANTS

A CONSORT diagram (Schulz et al., 2010) will be produced by/ in collaboration with the Trial Manager.

All baseline variables will be summarised by randomised group. Categorical data will be reported as frequencies (%) and continuous data will be reported as mean (SD) unless skewed then they will be reported as median (interquartile range). No statistical tests will be carried out.

13.1.2 PRIMARY OUTCOME ANALYSIS

The primary outcome is total tic severity score (TTSS) of the Yale Global scale (YGTSS) at three months post randomisation. This will be analysed using a linear regression model, including baseline TTSS and centre (the stratification variable). If the assumptions of linear regression are violated, another suitable method will be used. This will be analysed using intention to treat principles.

Analyses will be complete case. However, predictors of missingness will be examined. If any are found, then these will be modelled as a supportive analysis. There are no planned subgroup analyses.

13.1.3 SECONDARY OUTCOME ANALYSIS

Secondary outcomes will be analysed using similar statistical methods as the primary outcome. Continuous outcomes will be analysed with linear regression. Dichotomous outcomes will be analysed using logistic regression. These will be presented as estimates or odds ratios as appropriate and 95% CI (no p-values).

13.1.4 SENSITIVITY AND OTHER PLANNED ANALYSES

A supportive analysis of the primary outcome will include any predictors of missingness.

13.2 INTERIM ANALYSIS

There are no interim analyses planned, however this does not preclude the DSMB from requesting analyses.

14 QUALITATIVE METHODS

Interview data will be analysed using theme analysis (Braun and Clarke, 2006). Theme analysis has been selected as a flexible method of analysis which allows for both inductive (emerging from the interview text) and deductive (guided by theory) coding. Interviews will be recorded and transcribed verbatim. A random selection of interview transcripts (25%) will checked against the original recorded interview for accuracy. Data will be analysed using NVivo to establish themes and subthemes. A codebook describing the themes will be constructed as recommended by Boyatzis (1998) and an independent researcher will be asked to code a selection of text extracts to establish the trustworthiness of themes. Agreement of 70% or more will be considered acceptable. A mixed-methods approach will be used to integrate qualitative and qualitative data in order to explore the fully explore implementation of the intervention.

15 ECONOMIC EVALUATION

The primary cost-effectiveness analysis for the within-trial evaluation will be the mean incremental cost per point change in YGTSS of TAU plus BiP-Tic compared to TAU plus online education with therapist support at 3 months, from an NHS and personal social services cost perspective. A secondary analysis of the mean incremental cost per quality-adjusted life-year (QALY) of TAU plus BiP-Tic compared to the active comparator over 18 months from a health and social care cost perspective will also be calculated. QALYs will be calculated from patient level responses to the Child Health Utility 9D (CHU9D) and associated algorithm (Stevens, 2012). The area under the curve will be calculated using utilities scores derived from the CHU9D at baseline and each follow-up. The regression analysis will include treatment group, baseline utility scores for baseline adjustment and centre as a fixed effect. Predictors of missingness will be also included in the regression analysis.

To calculate the mean cost per patient of BiP Tic plus therapist support we will collect detailed information on therapist time and evaluate the cost of ongoing maintenance and support for the website. The cost to develop the website will not be included as it is considered a sunk cost. We will collect information to estimate the cost of implementation (changes required to services including staff training and IT infrastructure that may need to be implemented). Similar information will be collected on the active comparator. To establish the cost of TAU and other health care costs related to TS in both the intervention and comparator arms additional health and social care resource use will be obtained from a modified version of the CSRI which also combines elements of the Child and Adolescent Service Use Schedule (CA-SUS) (Byford et al., 2007) completed by parents. Unit costs will be taken from national published sources.

For each resource use item we will report descriptive statistics for the percentage number of patients that accessed the service and the mean and standard deviation of times they accessed.

To calculate the incremental mean cost of health and social care of TAU plus BiP TIC compared to TAU plus active control we will adjust for baseline CSRI costs and include centre as a fixed effect. Predictors of missingness will also be included in the regression analysis.

As part of the secondary analyses we will include cost of education and out of pocket costs.

To calculate the cost per point change in YGTSS the analysis of the YGTSS will exactly replicate the analysis of the primary outcome to ensure the results are the same.

We will report bootstrapped 95% confidence intervals for the primary and secondary analyses. The output from the bootstrapping will also be used to construct cost-effectiveness acceptability curves and cost-effectiveness planes. These will report the probability that BiP TIC is cost-effective compared to online education with therapist support for a range of values of willingness to pay for a QALY and for a point change in YGTSS.

A decision model projecting costs and QALYs into adulthood will also be developed. QALYs will be linked to changes in YGTSS and projected over time using a patient level simulation. An important piece of information collected as part of the trial will be what TAU in the NHS looks like for children with TS. Further consideration will also be given to the cost impact of implementing different service models to BiP-Tic for TS in the NHS and the corresponding costs and effectiveness as taken from the literature, The cost per QALY gained over the long term time horizon for different service models will be reported and compared with BiP-Tic and TAU based on net monetary benefit (NMB) for a range of values of willingness to pay for a QALY gained. An analysis plan for the decision model will be developed to provide additional information.

16 NAME OF COMMITTEES INVOLVED IN TRIAL

There are three committees in place to oversee the trial, including: a Project Management Group (PMG), Trial Steering Committee (TSC) and Data Safety and Monitoring Board (DSMB).

Project Management Group (PMG): The full PMG consist of all the co-investigators listed on the protocol and a representative from the Young Person's Panel. The PMG will meet at least every six months to discuss the study progress and overall conduct of the trial, including before any TSC meeting and at the end of the internal pilot to discuss study progression. As a minimum requirement the group will include Chief Investigator, the Trial Manger, a statistician, and the two therapist leads and a member of the operations team from Priment. Where people cannot attend in person, teleconference and Skype facilities will be provided.

Smaller team meetings will be held as required, but as a minimum, every month, with the Chief Investigator and the Trial Manager to discuss study progress.

Trial Steering Committee (TSC): The role of the TSC will be to provide overall supervision for a trial on behalf of the Trial Sponsor and Trial Funder and to ensure that the trial is conducted to the rigorous standards set out in the Medical Research Council's (MRC) Guidelines for Good Clinical Practice. The TSC will specifically review: trial progress, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question, the safety and well-being of the trial participants. The TSC will meet annually with one meeting coinciding with the end of the internal pilot (January 2019), to determine whether the trial should continue. The TSC consists of an independent chair, statistician, PPI member, the Sponsor, two clinical experts and one clinical director.

Data Safety and Monitoring Board (DSMB): The DSMB is the only body involved in a trial that has access to the un-blinded comparative data. The role of its members is to monitor these data and make recommendations to the TSC on whether there any ethical or safety reasons why the trial should not continue. The safety, rights and well-being of the trial participants will be paramount. The DSMB will consider the need for any interim analysis advising the TSC regarding the release of data and/or information. The DSMB may be asked by the TSC, Trial Sponsor or Trial Funder to consider data emerging from other related studies. If funding is required above the level originally requested, the DSMB may be asked by the Chief Investigator, TSC, Trial Sponsor or Trial Funder to provide advice and, where appropriate, information on the data gathered to date in a way that will not compromise the trial. The DSMB will meet annually, shortly before the TSC meeting. One DSMB will coincide with the end of the internal pilot (December 2018), to determine whether the trial should continue. The members of the DSMB are completely independent of the trial and consist of an independent chair, statistician, and clinical expert.

17 RECORDING AND REPORTING OF ADVERSE EVENTS AND REACTIONS

17.1 DEFINITIONS

Term	Definition
Serious Adverse Event (SAE)	Any untoward occurrence that: • results in death, • is life-threatening, • requires hospitalisation or prolongation of existing hospitalisation, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect

	• is otherwise considered medically significant by the investigator
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Any SAE that is deemed to be • Related to the trial intervention AND • Unexpected (not listed in the protocol as an expected side effect of the intervention)

17.2 EXPECTED SIDE EFFECTS

The following are a list of expected adverse events that have been noted in a previous Swedish pilot study of BiP Tic:

- Increased anger/outbursts/disruptive behaviour
- Increased irritability
- Increased depressed mood
- Increased anxiety/stress
- Increased tics
- Increased tiredness/fatigue
- Headaches
- Increased/decreased sleep

It is important to note that all the side effects may also be symptoms of the underlying condition, rather than the intervention itself. Side effects will be closely monitored by the therapist and reported in accordance to the procedures outlined in this protocol and also by the research team through the adverse events form. It is also likely that participants in the trial will be receiving medication as a result of their tics or co-morbid health conditions, any adverse event/side-effect that is caused by their medication will not be considered as an adverse event/side-effect of the intervention. This will be determined by the CI who is a Consultant Child and Adolescent Psychiatrist using the guidance outlined in Section 18.4, A 'Related Events'. A list of their current medications/interventions is collected at each time point.

17.3 RECORDING ADVERSE EVENTS

All adverse events (AE) will be recorded in the medical records, CRFs or other designated place following consent. All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate. All

adverse events will be recorded until the six month follow-up (three months after the end of treatment).

The therapists and researchers will be recording any AE noted through their communications with the patient and that noted on the adverse event form and record any serious adverse events on the Priment safety report form. The adverse event form is collected at baseline (to determine baseline presence of any issues; these will not be taken as an AE to the treatment since it is completed prior to treatment initiation). The adverse event form will then be completed at mid-treatment follow-up and end of treatment follow-up at 3-6 months.

Once completed, the adverse event forms will be reviewed by the research team to identify any SUSARs. If an event meets the definition of a SUSAR (See table above) then the member of staff that received the information will follow the reporting procedures as defined in section 18.5.

If the event is listed above as an expected event, then this does not need to be reported.

Additionally, a measure of low mood (MFQ) is completed throughout the study and includes a question on suicidality. Scores on this suicidality question can raise a flag in the BASS system. If this occurs, the therapist will advise the participant to consult their GP and/or specialist Trust clinician if they are concerned.

Researchers and therapists will also be trained in safeguarding procedures as part of the Site Initiation meeting. Safeguarding issues will be recorded and reported in accordance with the guidance outlined in the trial SOP “safeguarding procedures”. The SOP documents issues around disclosure, confidentiality, reporting processes and informing the relevant ORBIT team members and legal authorities.

17.4 ASSESMENTS OF ADVERSE EVENTS

A. RELATED EVENTS

The assessment of the relationship between adverse events and the administration of the intervention is a decision based on all available information at the time of the completion of the case report form. If the event is a result of the administration of any of the research procedures then it will be classed as related.

B. EXPECTED EVENTS

If the event has been listed in the protocol (section 18.2) as an expected side effect of the intervention then the event will be classed as expected. If the event is not listed then it will be classed as unexpected.

17.5 PROCEDURES FOR REPORTING SERIOUS ADVERSE EVENTS

The reporting of adverse events will be completed according to Priment non-CTIMP safety management SOP.

The Chief Investigator (and medical expert) will assess the event for seriousness, expectedness and relatedness to the trial on a case-by-case. The person to whom the event was disclosed to will be responsible for providing all necessary information to the CI and the clinical research lead at each site may be involved in these discussions. The CI will then take appropriate medical action, which may include halting the trial and informing the Sponsor of such action. If the event is deemed serious, unexpected and related to the trial treatment or intervention they shall inform the REC using the reporting form found on the HRA web page within 15 days of knowledge of the event, and include the Sponsor (Nottinghamshire Healthcare NHS Foundation Trust) and Priment in all communications. They shall, within a further eight days send any follow-up information and reports to the REC and make any amendments as required to the study protocol and inform the REC as required.

All SUSAR will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study treatment / intervention is not the cause.

Any participant who experiences an SUSAR may be withdrawn from the study at the discretion of the investigator and the Sponsor. Every withdrawal will be examined by the Trial Steering Committee (TSC). The TSC will be made aware of all serious adverse reactions/SUSARs.

The CI will have responsibility for informing the other site/therapists of the SUSAR and any relevant safety information, which may be delegated to the Trial Manager (Charlotte Hall). The CI will also inform the local clinical care team (CAMHS or Community Paediatrics) or GP under which the participant is routinely seen for of any SUSARs (details of which are obtained at screening/referral).

17.6 THE TYPE AND DURATION OF THE FOLLOW-UP OF PARTICIPANTS AFTER ADVERSE EVENTS

Adverse events will be recorded for the 6-month follow-up period, which equates to the time during which the intervention is taking place. Participants' local GP will be informed of any SUSARS. This local team will be responsible for any routine follow-up care. If requested by the local team, consultation with the study CI (and medical expert) would be provided.

17.7 ANNUAL PROGRESS REPORTS

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The Chief Investigator and Trial Manager will prepare the APR.

17.8 REPORTING URGENT SAFETY MEASURES

If any urgent safety measures are taken, the PI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to REC of the measures taken and the circumstances giving rise to those measures.

17.9 NOTIFICATION OF SERIOUS BREACHES TO GCP AND/OR THE PROTOCOL

For the purpose of this protocol we define a "serious breach" is a breach which is likely to affect to a significant degree –

(a) The safety or physical or mental integrity of the participants of the trial; or

(b) The scientific value of the trial.

The Chief Investigator or Trial Manager will immediately notify the Sponsor of any case where the above definition applies during the trial conduct phase. Priment's SOP on 'serious breaches' will be followed.

The CI and Sponsor will work together to identify the extent of the breach and to determine what urgent safety measures are required. The CI and Sponsor will devise a formal plan of corrective action to address the breach. Depending on the assessment of seriousness and impact, the Sponsor may decide to carry out a full audit of the trial and the trial management systems/ procedures.

The sponsor of the trial will notify the REC in writing of any serious breach of (a) the conditions and principles of GCP in connection with that trial; or (b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach. Reports of serious breaches will give details of when the breach occurred, the location, who was involved, the outcome and any information given to participants. An explanation as to the cause of the serious breach will be given and the main REC informed what further action the sponsor plans to take.

18 MONITORING AND INSPECTION

A monitoring plan will be established for the trial based on the risk assessment. The trial will be monitored with the agreed plan.

The investigator(s)/ institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

19 ETHICS AND REGULATORY REQUIREMENTS

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Mental Capacity Act 2005. The sponsor and Priment will ensure that the trial protocol, patient information sheet, consent form, letter to usual treating clinician, and submitted supporting documents have been approved by the appropriate regulatory bodies, prior to any participant recruitment. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation. Ethical approval will be granted before enrolment of the first participant. The Chief Investigator, supported by the Trial Manager, will ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual participant. Within 90 days after the end of the trial, the CI/Sponsor will ensure that the main REC is notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the Sponsor with a summary report of the clinical trial, which will then be submitted to the main REC within 1 year after the end of the trial.

The issue of consenting children and young people is a specific ethical considerations to this trial. Consent will be obtained from all participating young people aged 16 years and over, and parents/carers of all participating young people, and assent will be obtained from young people under the age of 16 years. If the researcher perceives a conflict between the parent/carer and the child/young person with regards to participation, the patient will not be entered into the trial. Age-appropriate information sheets have been created for children and young people to aid in providing informed consent. Parents/cares and children/young people will be encouraged to discuss any questions or concerns about trial participation with the researcher before consenting. Patients (and their families) will have at least 24 hours to consider participation after reading the initial information sheets. Participants will be made aware of their right to withdraw at any point during the trial through the information sheet.

19.1 PUBLIC AND PATIENT INVOLVEMENT

Design of the research

In developing this application, we have conducted a number of Patient and Public Involvement (PPI) activities, which included focus groups with young people and their parents and a pilot study where five young people with TS and their parents were given a

prototype digital platform containing video and text content about TS to use for 2 weeks and then participated in focus groups. From this, we learnt that young people and their parents are enthusiastic about digital interventions for tics that allow them to manage tic-related distress during daily life. They liked being able to rate their tics and detect patterns. They particularly liked the idea of having access to help and information on their own device at a time they chose in addition to remote therapist support. This feedback informed our proposal to evaluate a therapist-guided, remotely delivered behavioural intervention that young people could use at home, supported by their parents.

Additionally, the intervention was co-designed through PPI input. In Sweden, focus groups were conducted with five families with children with TS to aid the design of the intervention. After the Swedish pilot study of BiP Tic, qualitative interviews were conducted with participating families. These families provided comments on what they liked/didn't like and suggestions for improvement. This feedback was used to create the new English version of BiP Tic. Additionally, the English version of both the BiP Tic intervention and the online education was reviewed by PPI members (including parents and children/young people with tics) in England, and their suggestions were used to refine the interventions.

We also developed a study logo with our PPI group, this logo is included on the participant information sheets.

Involving people with experience of TS is vital to develop an intervention that people will want to use and to design an evaluation inclusive of the perspectives of patients and parents or carers. Effective involvement also mitigates the risk of the research failing because of poor engagement with the intervention, poor recruitment to the trial or limited uptake in real-world practice.

The problem of lack of access to evidence-based behavioural treatment for tics was identified in the HTA Evidence Synthesis (Project 10/142/01): Clinical effectiveness and patient perspectives of different treatment strategies for tics in children and adolescents with TS (Hollis et al., 2016). Two patients were part of the project steering group and participated in the prioritisation of research recommendations, which included developing and evaluating a remote digital behavioural intervention for tics.

Management and undertaking the research

Involvement in this study will be supported and facilitated by co-applicant Dr Susan Brown, involvement lead for the NIHR MindTech Healthcare Technology Co-operative (HTC). We also have excellent links with Tourette's Action (TA) (Suzanne Dobson) who have actively engaged in the development of this proposal and will continue to support us with recruitment, and dissemination and implementation at scale.

Young People's Panel (YPP): We have set up a Young People's Panel (YPP), which consists of 11 patient and public involvement (PPI) members, 5 young people with TS, 5 parents of young people with TS, and 1 experience PPI involvement member of a child with neurodevelopmental disorders. The panel are invited to our project management group (PMG) team meetings and have provided support to shape the design of the 'co-design and optimisation' phase of the study, experimental design and recruitment strategy. They will continue to support in recruitment strategies throughout the study and in the interpretation and dissemination of findings. A member of the young person's panel and their parent has gone through the intervention and the screening/assessment procedures as a mock participant and provided feedback to improve the protocol. We will continue to recruit to this panel throughout the study, to ensure wide representation of the needs of young people living with TS.

The PPI group have provided input on all our patient-facing documents, including: the PIS, consent forms, WebEx and BiP guides. Refinements and alterations were made based on their suggestions. These included suggestions from both parents and young people. Additionally, parents and young people reviewed our selection of outcome measures to ensure we captured measures that were important to the families whilst not being overly burdensome. Families noted that they would want to know what to do if their child answered questions on the MFQ which indicated they were of low mood. As a result of this input we also made the decision to include an automatic message in the BASS system after measurement completion to direct families in the direction of appropriate healthcare support if they feel it is necessary.

Involvement in the Trial Steering Committee: An independent PPI member has been identified to sit on the Trial Steering Committee (TSC) to aid oversight and governance of the study. We will ensure effective mechanisms are in place to enable close communication between the Young People's Panel and the TSC and that our PPI member of the TSC is well supported. Tailored learning opportunities and support will be developed in response to the needs of the individual young persons and a budget has been included for this. Involved patients and parents will also benefit from peer support of the experienced members of the NIHR MindTech HTC Involvement Team.

Analysis of results and dissemination of findings

Our PPI panel will play a pivotal role in the dissemination of findings. The PPI group will be involved in interpretation of results as part of their role in the PMG. The PPI group will provide advice and oversight in writing findings in a lay-friendly format, and we shall use our links with TA to disseminate the findings to patient and public members.

We are keen to keep members of the public updated with the trial progress. Using our established links with Tourette's Action we will report anonymous testimonials (with

permission of the participant) on the Tourette's Action website to feedback to other people with tics about what it is like being part of the ORBIT trial.

20 FINANCE

The study was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) for £1,568,192. The funding started on 1st October 2017 and continues for 4 years. The costings include costs for higher education institution costs, NHS costs, and other organisation costs. There is a fully costed PPI budget. Further details on the finances are available on request to the CI.

21 INSURANCE

Nottinghamshire Healthcare NHS Foundation Trust (NHCFT) holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in an NHS organisation or an organisation contracted to the NHS, an NHS organisation or an organisation contracted to the NHS continues to have a duty of care to the participant of the clinical trial. NHCFT does not accept liability for any breach in the NHS organisation or an organisation contracted to the NHS's duty of care, or any negligence on the part of NHS organisation employees. This applies whether the NHS organisation is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of NHCFT or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

NHS organisation selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to NHCFT, upon request.

22 PUBLICATION POLICY

The inclusion of NHS researchers to deliver the treatments should help to immediately disseminate the clinical approach. In addition, we have a strong track record of such dissemination, which has been achieved through a systematic approach of delivering clinical training workshops supported by Tourette's Action, the British Association for Behavioural and Cognitive Psychotherapies, Royal College of Psychiatrists, European Society for the

Study of Tourette syndrome, and British Association of Psychopharmacology. We have extensive links with organisations concerned with implementation including NIHR CLAHRCs and Academic Health Science Networks (AHSNs). The NIHR MindTech Healthcare Technology Co-operative (Director; Hollis) provides national leadership in the development, evaluation and implementation of innovative digital technologies for mental healthcare. We have a strong track record of high impact peer-reviewed publications; this research will result in numerous such papers. A full and complete account of the research will be published in the NIHR HTA Journal. In addition we will present the findings at national and international conferences, as well as service user / voluntary sector organisations such as Tourette's Action utilising newsletters, websites and social media. The NHS will be the primary consumer of this research and we will hold focussed events for NHS providers, commissioners and training organisation. We have an excellent track record in conducting research which has been directly relevant to service delivery including working with NHS commissioners (in collaboration with the AHSN East Midlands) to assess value and promote adoption of new digital technologies in healthcare.

Our focus on increasing access to evidence-based interventions via digital technology is clearly consistent with NHS priorities and needs and has the potential to be applied to increasing treatment access for a wider range of mental health problems in young people associated with significant personal, social and economic costs. The trial will generate data that is required for commissioners and policy makers regarding patient preferences, valued outcomes, and cost-effectiveness of therapist-supported digital interventions, which will inform evidence-based commissioning of services.

All proposed publications will be approved by the NIHR and Priment prior to publishing. We will follow Priment SOPs with regards to publishing.

23 STATEMENT OF COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the UK Regulations, EU GCP and the applicable regulatory requirement(s).

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