NICE National Institute for Health and Care Excellence

**Medical technologies advisory committee (MTAC)**

**15 August 2024**

# Information pack for draft guidance considerations on Digitally enabled therapy for chronic tic disorders and Tourette Syndrome

This product was selected for early value assessment in 2023. Clinical and economic evidence has been submitted to NICE by the companies, and an external assessment centre report has been completed.

This pack presents the information required for the MTAC to make draft recommendations on this topic. The consultation period on these draft recommendations is scheduled to take place between 19 November 2024 and 17 December 2024.

## Guidance lead team

| | |
|---|---|
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**Papers included in pack:**

1. Front sheet
2. Scope

3a. Submission from Tourettes Action

3b. Patient survey report (presentation slides)

4. EAG assessment report (EAR)
5. EAG assessment report overview (ARO)
6. Stakeholder comments & EAG responses on the EAR
7. Register of interests

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HealthTech Guidance

# GID-MT605 Digitally enabled therapy for chronic tic disorders and Tourette Syndrome

# Final scope – updated

April 2024

## 1 Technologies

### 1.1 Purpose of the technologies

NICE is evaluating the possible cost and clinical effectiveness of digitally enabled therapy as an intervention for people with chronic tic disorders and Tourette Syndrome. This is due to the potential benefit of digitally enabled therapy in addressing the significant unmet needs of the population. Current guidance recommends that children or young people with tic disorders, that significantly interfere with their ability to function in their daily lives, should be referred to specialist mental health services, neurodevelopmental teams or for neurological assessment (NICE Guideline 127, 2023). Adults with a tic disorder should be referred for psychological therapy if the disorder is troublesome, or accompanied by additional progressive neurological symptoms (NICE Guideline 127, 2023)

Accepted evidence-based treatment options for diagnosed tic disorders are psychoeducation as a first line and behavioural therapies for those who continue to report difficulties with their tic disorder. For some people behavioural approaches may not be as effective, feasible or accessible and medications will be discussed as a possible treatment option with or without behavioural therapies.


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Behavioural therapies for tic disorders include habit reversal therapy, comprehensive behavioural intervention for tics (CBIT) and exposure and response prevention therapy (ERP). However, due a shortage of trained therapists, behavioural therapy is only being offered at a small number of specialist treatment centres. As a result, experts estimate less than 20% of children and young people with tic disorders currently have access to behavioural therapies (Marino et al, 2023). Due to the varied expertise, access and availability of services across the UK, digitally enabled interventions may improve access as well as equity of access to treatment options for people with tic disorders.

## 1.2 Description of the technologies

The scope focuses on digitally enabled therapies intended for children and young people with tic disorders that:

- Have appropriate regulatory approval or are actively working towards regulatory approval, for example CE mark / UKCA mark and DTAC compliance
- Are available or working towards being available to the NHS
- Have online guided contact with a practitioner as part of the programme, or clinician oversight with the intervention for user safety.

In total 2 digitally enabled technologies for chronic tic disorders have currently been identified as in scope:

**Online Remote Behavioural Treatment for Tics**, **ORBIT (Mindtech)** is an online therapeutic intervention which aims to reduce tic severity in children and young people with tic disorders. The ORBIT treatment programme was developed from a previous platform (BIP TIC) in Sweden. ORBIT provides a form of behavioural therapy called exposure and response prevention (ERP), which is guided with an online therapist across a 10-week program. It is delivered on a secure internet platform and includes self-help guided chapters including chapters covering tic psychoeducation followed by exposure and response prevention behavioural therapy tasks. It also includes separate chapters for parents and care givers to further


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support their role. The programme teaches users to suppress their tics while tolerating the urges to tic. The therapist has 10 to 20 minutes of contact time with the family each week and promotes engagement with the intervention as well as answering any questions. ORBIT has been studied as part of National Institute of Health and Care Research (NIHR) funded UK based trials, which have reported it to be a clinically and cost-effective intervention at up to 18 months (Hollis et al, 2021, Hollis et al, 2023). ORBIT does not require CE marking as it is not considered a software as a medical device. The company are working towards DTAC compliance currently as part of the NIHR Invention for Innovation Programme.

**Neupulse (Neurotherapeutics)** is a wearable digital wrist device which uses a novel approach utilising neuromodulation to produce median nerve stimulation (MNS). The device is reported to result in a reduction in tic frequency, tic severity and associated urges both whilst the device is active and in a follow up period without device activated (pre-publication available Morera et al, 2023).

The device requires no active effort by the user but worn when the user wants to feel more control of their symptoms. It is proposed for children and young adults aged 12 and over (due to the size of the wrist) as well as for adults with suspected or diagnosed Tourette Syndrome or a chronic (motor or vocal) tic disorder. Guidance alongside the device will include written and video-based material and a technical support helpline. The device has a corresponding phone app which can be used to generate a document of changes in symptoms for clinical oversight.

Neupulse is currently in further development and working towards CE and UKCA marking. It is estimated that the device will be available in 2026 (depending on regulatory approval). Evidence has been collected as part of a UK parallel double-blind sham-controlled trial for the reduction of tics in individuals with tic disorder (pre-publication available Morera et al, 2023).


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# 2 Relevant conditions

These technologies are intended for people who have diagnosed chronic primary tic disorders. Tics are fast, repetitive muscle movements that result in difficult to control body movements or sounds. This can be described as an unpleasant sensation, commonly called an “urge” that only goes away when the tic is performed. Tics may involve body movements (motor) or sounds (phonic), or both. Examples of tics might include blinking, grimacing, head jerking, head banging, finger clicking, coughing, grunting, sneezing, repeating a sound or phrase (in approximately 10% of people this can be something offensive, such as swearing). The body movement or sound produced are the visible aspect of tics, but people describe many tics that are not visible to others. Tics are commonly associated with anxiety disorders. They can also lead to significant pain and discomfort which may worsen with tiredness or at times of high emotion such as stress.

Primary tics are more common in boys than girls (at a ratio of 4 to 1). Typically, primary tics begin between 4 and 6 years of age, can peak in early adolescence and decrease naturally into early adulthood. However, for a minority of adults their tic disorder does not reduce significantly, and some continue to experience a severe and debilitating form of tic disorder. It is common for people with Tourette syndrome to have comorbidities, with some studies reporting up to 90% of the population presenting with one or more co-occurring condition (Eapen at al, 2022). These may include neurodiverse conditions such as attention deficit / hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD) and autism spectrum disorder (ASD) as well as anxiety disorders and feelings of low mood and depression. The impact of tics can be variable, affecting academic, social, occupational, and physical functioning. Young people with tic disorders commonly report extensive stigma, feelings of isolation and bullying. Without adequate support tic disorders can significantly affect various aspects of the person’s life, contributing to a reduced quality of life. Having long-standing tics is also associated with a reduction in life expectancy and a fourfold increased risk of death by suicide (Marino et al, 2023).


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# 3 Current management and care pathway

Currently there is no clinical guideline for the assessment and treatment of tic disorders in the UK. Guidelines have been published recently from the European Society for the study of Tourette syndrome (ESSTS) (Muller-Vahl et al, 2023) and BMJ best practice for tic disorders (Pringsheim, 2022) and Tourette's syndrome (Grados, 2023) see Appendix A.

Symptoms of tics may be identified by the person themselves, by parents, carers, peers or in school settings. For children and young people presenting in primary care a watch and wait approach is typically taken for those with simple tics without functional impairment (NG127).

For people who are having difficulties with a tic disorder a referral should be made to an appropriate secondary or tertiary service (depending on the presentation, comorbidities, and local specialist clinics). Referrals may be made to mental health services, neurodevelopmental teams, paediatric or neurology teams dependent on local services.

Diagnosis should be made by a comprehensive clinical history as well as a general medical and neurological examination. Tic disorders are classified according to the type of tic present and the duration of the tics. Tics can be categorised as functional tic-like behaviours or primary tics (also known as neurological tics). Functional tics can start suddenly with no apparent cause, it is common for them to present as complex tics initially and more often are associated with anxiety. Primary tics tend to present as simple tics initially and become more complex over time.

Tics can be transient, lasting less than 1 year, commonly known as provisional tics. Or they can persist over a year and be classified as a chronic tic disorder (when either motor or vocal tics are present). When both motor and vocal tics are present for more than 1 year, this is commonly known as Tourette syndrome. In the UK, Tourette Syndrome is identified in 1 per 100 school children (BMJ, 2023).


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Initial intervention for all tic disorders is psychoeducation. This should be extended to family, teachers, and peers in order to reduce any associated stigma and distress. For some people no further treatment will be needed.

Assessment of possible comorbid disorders should also take place with consideration of their possible contribution in impacting functional capacity at home, school, in the workplace and with peers (BMJ, 2023). If other conditions are present referral to a psychiatrist may be appropriate for further evaluation and treatment.

For those who continue to have bothersome tics despite psychoeducation, further treatment is indicated. Current evidence-based options include behavioural therapies with or without medication. Evidence based cognitive behavioural approaches should be the first line for children and young people, these include: comprehensive behavioural intervention for tics, habit reversal therapy, and exposure and response prevention therapy. Experts advised that children aged 8 and under typically are unlikely to be able to reliably identify urges, which is required to have positive outcomes with behavioural therapy.

Medication should be considered if behavioural interventions have not been effective or have been deemed inappropriate. There are a number of pharmacological options which may be prescribed with or without continued therapeutic intervention. Treatment must be tailored to each individual's needs (BMJ, 2023).

More novel treatment options are being studied for tic disorders, including Median Nerve stimulation and deep brain stimulation. However an NHS England review of the evidence base for deep brain stimulation as a treatment option for adults with refractory Tourette Syndrome concluded that there is not sufficient evidence to support its routine commissioning (NHS England, 2018).


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# 4 Scope of the assessment

This evaluation is for people with chronic tic disorders and Tourette Syndrome who continue to report bothersome tics after initial psychoeducation. This evaluation does not consider provisional tics or functional tics, except for those that occur alongside primary tics.

**Table 1 Decision problem**

| | |
|---|---|
| **Decision question** | Does digitally enabled therapy for people with chronic tic disorders and Tourette Syndrome represent a clinically and cost-effective use of NHS resources? |
| **Population** | People with a diagnosed primary tic disorder that have had access to psychoeducation, however their tics continue to be bothersome to them.<br>Children and young people aged 12 and over are indicated for Neupulse. |
| **Subgroups** | If the evidence allows, the following subgroups may be considered:<br>• Children and young people<br>• Adults<br>• People with diagnosed comorbidities including: Attention deficit / hyperactivity disorder (ADHD), autism spectrum disorders (ASD)and obsessive compulsive disorder (OCD), anxiety disorders and depression. |
| **Interventions (proposed technologies)** | • ORBIT (MindTech)<br>• Neupulse (Neurotherapeutics)<br>These interventions should only be considered provided the person (and parent or carer where appropriate) have had access to a form of psychoeducation. If the tic disorder continues to cause difficulties for the person, a clinician may consider referring for these proposed interventions.<br>The Neupulse device is currently intended for use in adults and children aged 12 or over. |
| **Comparator(s)** | Standard care should include psychoeducation and face to face behavioural therapy. However, there may be a considerable waiting time, distance to travel or lack of access to specialist behavioural therapy. |
| **Healthcare setting** | Secondary or tertiary care settings, which may include children and young people's mental health services (CYPMHS), community mental health teams (CMHTs), community paediatrics, secondary care paediatrics, neurology or neurodevelopmental teams including neurologists, neuropsychologists, psychiatrists and psychologists. |
| **Outcomes** | Outcome measures to consider include:<br>**Intermediate measures**<br>• Intervention related adverse events |


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| | |
|---|---|
| | • Treatment satisfaction and engagement<br>• Intervention adherence, rates of attrition and completion<br><br>**Clinical outcomes**<br>• Measures of symptom severity (self, parental or practitioner reported) such as YGTSS, TTSS, CGI-I, CGAS, PUTS-9, Parent tic scale<br>• Tools for depression and anxiety such as Patient Health Questionnaire for adolescents, Childrens depression inventory and the Beck depression inventory<br>• Social, behavioural, and functional outcomes including measures such as educational attendance and attainment and work engagement<br>• Suicidal thoughts and behaviour, adverse events.<br><br>**Patient reported outcomes**<br>• Health related quality of life such as GTS-QOL, pain and sleep measures<br>• Patient experience and satisfaction<br>• Rates and reasons for adherence / attrition.<br><br>**Costs** will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include:<br>• Cost of technologies, including licensing fees<br>• Cost of other resource use (associated with managing tics, adverse events or complications) including:<br>– GP appointment, mental health support team / CYMHS appointments<br>– Health care professional training, grade, and time for providing regular support and guidance for the users of the digitally enabled technologies.<br>Any economic data on technologies cost effectiveness, ICER statistics will be considered if reported. |
| **Economic analysis** | A health economic decision model will be developed comprising a cost effectiveness analysis.<br>Costs will be considered from an NHS and Personal Social Services perspective.<br>Sensitivity and scenario analysis should be undertaken to address the relative effect of parameter or structural uncertainty on cost-comparison estimates.<br>The time horizon should be long enough to reflect all important differences in costs or outcomes between the technologies being compared. |


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## 4.1 Other issues for consideration

- Technologies are heterogenous in various ways including:
  - Type of intervention: Behavioural therapy (ERP in ORBIT). Behavioural therapy is an evidence-based treatment option for tic disorders. Median nerve stimulation (used in Neupulse) remains a novel approach.
  - Technologies are at different stages in development (Neupulse is still in development), which will impact on the levels of evidence currently available and vary the evidence of use in the NHS. This assessment will look across a range of evidence types including evidence of clinical effectiveness.
  - Delivery mode (computer, app, wearable devices), access (referred or self-referrals), intended population (varies in age groups and exclusion criteria), practitioner or parental supported, having therapist guidance, data that has been collected and current regulatory status all vary across the technologies.

- Given the large differences in interventions and approaches consideration must be given to the service costs, workforce burden, set up and maintenance costs as well as software update requirements for each individual intervention.

- A large proportion of this population are likely to have additional diagnosed or undiagnosed neurodevelopmental conditions including OCD, ADHD and autism spectrum disorders (ASD).

- People with chronic tics are at higher risk of death by suicide.

## 4.2 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

- Tic disorders is more common in boys than girls at a ratio of 4:1


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- Patient-facing digital health technologies may be unsuitable for people with cognitive impairment, problems with manual dexterity or learning disabilities. Carer or advocate assistance may be required to navigate the program and consideration of this should be made by the company as well as the referring practitioner when considering appropriate intervention for the child or young person. Further considerations can be found in NICE Guidance on mental health problems in people with learning disabilities (NG54, 2016).

- People, or their families / carers, with English as a second language may have difficulties navigating digital technologies provided in English.

- Peoples ethnic, religious and cultural background may affect their views of digital health interventions. Healthcare professionals should discuss the language and cultural content of digital health interventions with users before provision.

- People from lower socioeconomic backgrounds may find it difficult to engage in therapeutic material given the time demands of the programs.

- Patient facing digital health technologies should ensure their program is accessible for screen readers (people with visual impairments) and those with hearing impairments.

- Specific groups may particularly benefit from improved access to online behavioural therapy, for example:
  - Those living in areas not currently served by specialist clinical centres might have difficulty travelling to face-to-face appointments if public transport is unreliable, costly and if parents are unable to drive them.
  - Adolescents may have an increased engagement with this format of intervention.


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  - People from lower socioeconomic groups may lack the financial support required to ensure that they attend face to face sessions.

  - Some children and young people may not have the family support needed to ensure that they attend face to face sessions. These children and young people may also have less support to seek help in the first place or to navigate the healthcare system.

- However, accessibility would not be improved for those who are unable to engage with a digital service due to a lack of equipment, unavailability of internet connection or lack of experience with computers or lack the privacy needed to complete this intervention. Additional support and resources may be needed for these individuals.

Chronic tic disorders and Tourette Syndrome can significantly affect people's daily living. Under the Equality Act 2010, a person has a disability if they have a physical or mental impairment that has a substantial and long-term effect on their ability to do typical day-to-day activities. Age, sex, disability, race and religion are protected characteristics under the Equality Act (2010).

## 4.3 Potential implementation issues

- The appropriateness of behavioural therapies or median nerve stimulation should be assessed on an individual basis.
- There is no national guideline in place for the treatment of tic disorders.
- There is high variation in services available to the population.

  Experts highlighted the importance that technologies have an online guided practitioner or clinical oversight, to ensure users had contact with a trained practitioner to promote engagement, motivation and accountability for improved outcomes. As well as being key for safety, in


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order to ensure users who are not receiving benefit can be identified and supported as required.

# 5 Stakeholders

## 5.1 Healthcare professional organisations

The following healthcare professional organisations have been identified as stakeholders for this evaluation:

- Academy of British Neurologists
- Association of Child Psychotherapists
- Association of Educational Psychologists
- British Academy of Childhood disability
- British Association for Counselling and Psychotherapy
- British Association of Occupational Therapists and College of Occupational Therapists
- British Psychological Society
- British Paediatric mental health group
- British Paediatric Neurology Association
- British Psychotherapy Foundation
- Primary Care Neurology Society
- Royal College of Paediatrics and Child Health
- Royal College of Psychiatrists
- Royal College of Speech and Language Therapists
- UK Council for Psychotherapy
- Society for coaching psychology
- National CAMHS Support service / Children and Young peoples mental health service (CYPMHS)
- British Psychoanalytic Council
- British Association for Behavioural and Cognitive Psychotherapies (BABCP)
- Association of Psychoanalytic Psychotherapy in the NHS
- Association for Child and Adolescent Mental Health


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- Counsellors and Psychotherapists in Primary care
- Mental Health nurses association
- Mental Health forum committee

## 5.2 Patient and carer organisations

NICE's Public Involvement Programme have identified the following patient and carer organisations for advice:

- Ambitious about autism
- Asperger foundation
- Autism East Midlands
- Autism Northern Ireland
- Challenging Behaviour Foundation
- Child autism UK (formerly known as Peach)
- National Autistic Society
- Mind
- Tourettes Action
- The Neurological Alliance
- The Brain charity

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April 2024


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## Appendix A Related Guidance

- Suspected neurological conditions: recognition and referral (NG127), NICE Guideline, October 2023.
- BMJ Best Practice, Tic disorders 2022 Pringsheim, T
- BMJ, Best Practice Tourette Syndrome, 2023 Grados, M.
- European Clinical guidelines for Tourette syndrome and other tic disorders version 2.0. Part I assessment. 2022. Szelko, N., Robinson, S., Hartmann, A., Ganos, C., Debes, N., Skov, L., Haas, M., Rizoo, R., Stern, J., Munchai, A. Czernecki, V., Dietrich, A., Murphy, T., Martino, D., Tarnok, Z., Hedderly, T., Muller-Vahl, K., Cath, D.
- European Clinical guidelines for Tourette syndrome and other tic disorders Part II, interventions. 2022 Andren, P., Jakubovski, E., Murphy, T., Woitecki, K., Tarnok, Z., Zimmerman-Brenner, S., van-de-Griendt, J., Mol Debes, N., Viefhaus, P., Robinson, S., Roessner, V., Ganos, C., Szejko, N., Muller-Vahl, K., Cath, D., Hartmann, A., Verdellen, C.
- European clinical guidelines for Tourette syndrome and other tic disorders- version 2.0. Part IV: deep brain stimulation 2022 Szejko, N., Worbe, Y., Hartmann, A., Visser-Vandewalle, V., Ackermans, L., Ganos, C., Porta, M., Leentjens, A., Mehkrens, J., Huys, D., Baldermann, J., Kuhn, J., Karachi, C., Delorme, C., Foltynie, T., Cvanna, A., Cath, D., Muller-Vahl, K
- Practice guideline recommendations summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders, 2019. Pringsheim, T., Okun, M., Muller-Vahl, K, Martino, D., Jankovic, J., Cavanna, A., Woods, D., Robinson, M, Jarvie, E., Roessner, V., Oskoui, M., Holler-Managan, Y., Piacentini, J.
- Canadian Guidelines for the Evidence-Based Treatment for Tourette Syndrome, 2012. Billinghurst, L., Carroll, A., Day, L., Dion, Y., Doja, A., Gorman, D., Luscombe, S., McKinlay, D., Pringsheim, R., Sandor, P., Steeves, T


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## Appendix B Abbreviations

| | |
|---|---|
| ADHD | Attention deficit / hyperactivity disorder |
| ASD | Autism spectrum disorder |
| CBIT | Comprehensive Behavioural Intervention for tics |
| CYPMHS | Children and young people mental health services |
| DTAC | Digital Technology Assessment Criteria |
| ERP | Exposure and response prevention therapy |
| ESSTS | European Society for the study of Tourette syndrome |
| ICER | Incremental Cost-Effectiveness Ratio |
| OCD | Obsessive compulsive disorder |
| PUTS | Premonitory urge of tics scale |
| TTSS | Total Tic Severity Score |
| YGTSS | Yale Global Tic Severity Scale |


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# National Institute for Health and Care Excellence
## Patient Organisation Submissions for Medical Technologies - Submission Template

### NICE Medical Technologies Advisory Committee

**Digitally-enabled therapy for tic disorders in children and young people**

**Please read the guide to completing a submission fully before completing this template.**

| Information about your organisation | |
|---|---|
| **Organisation name** | Tourettes Action |
| **Contact person's name** | Emma McNally |
| **Role or job title** | CEO |
| **Email** | [redacted] |
| **Telephone** | [redacted] |
| **Organisation type** | Patient/carer organisation (e.g. a registered charity) Y☐<br>Informal self-help group ☐<br>Unincorporated organisation ☐<br>Other, please state: |
| **Organisation purpose** (tick all that apply) | Advocacy Y☐<br>Education Y☐<br>Campaigning Y☐<br>Service provider ☐<br>Research ☐<br>Other, please specify: |

**What is the membership of your organisation (number and type of members, region that your organisation represents, demographics, etc)?**

We currently have 37,780 active contacts. We define someone as active when they have had contact with our services or been in contact with us in the last 3 years.

These active contacts are made up of roughly 22% professionals, such as medics, researchers and teachers, and 78% associates.

# National Institute for Health and Care Excellence
## Patient Organisation Submissions for Medical Technologies - Submission Template

These active associates include 7744 people who are a family member of someone with Tourette's and 3223 people who have Tourette's themselves.

In the most recent year ending 31st Dec 2023 almost 85,000 people sought information from our website, which provides a wide range of information to support people with TS, and we provided direct support and guidance to almost 2900 people through our helpdesk.

As a charity we support people across the UK (principally England, Wales and Northern Ireland). We are also often contacted by members outside of the UK looking for support and advice.

**Please note, all submissions will be published on the NICE website alongside all evidence the committee reviewed. Identifiable information will be redacted.**

If you haven't already, please register as a stakeholder by completing the stakeholder registration form and returning it to medtech@nice.org.uk

Further information about registering as a stakeholder is available on the NICE website.

Did you know NICE meetings are held in public? You can register on the NICE website to attend a meeting up to 20 working days before it takes place. Registration will usually close 10 days before the meeting takes place. Up to 20 places will be available, depending on the size of the venue. Where meetings are oversubscribed NICE may need to limit the number of places we can offer.

## Sources of information

**What is the source of the information about patients' and carers' experiences and needs that are presented in this submission?**

The information in this submission comes from a wide range of sources:

- A number of parents of children with Tourette Syndrome (TS), some who have been successful in accessing treatment and some who have yet been able to access any treatment
- A number of adults with TS
- Staff members from Tourettes Action who hear from our service users on a daily basis
- Staff members from Tourettes Action who either have TS themselves or have a child with TS
- Trustees from the Tourettes Action board who either have TS themselves, have a family member with TS or treat patients with TS in their clinics

# National Institute for Health and Care Excellence
## Patient Organisation Submissions for Medical Technologies - Submission Template

## Impact of the symptoms, condition or disease

**1. How do symptoms and/or the condition or disease affect people's lives or experiences?**

Tourette syndrome (TS) is a lifelong condition. It is a complex, genetically determined neurological disorder that typically starts around the age of 6/7 years and tends to peak around early adolescence. It affects all aspects of life, including social, physical and emotional aspects.

The peak in severity during early adolescence coincides with a time when children are often under many pressures usually trying to 'fit in' with their peers, whilst also juggling the stresses of puberty, peer pressure and school demands. The peak in their TS symptoms often adds to these strains, as the young people want to fit in, rather than feeling different and noticed by other people as being different.

Educational Impact

Whilst Tourette's does not directly impact a person's intellectual capability, it can, however, affect a person's ability to learn and focus on tasks, especially when in a group environment. In school, focus is often given to suppressing their tics, which in turn means that they can't focus entirely on the lesson. Tics can sometimes interrupt lessons and distract other students, which can then affect the self-image and self-confidence of children with TS. Many young people report that they find it difficult to make friends because of social anxiety around how people will react to their tics. This in turn can lead to social isolation, which can then result in bullying and victimisation and subsequent mental health difficulties can be reported as a result of this. Children and young people with Tourette's often receive a lower-than-expected academic attainment. This under performance can be as a result of missed days at school. The missed schooling, can be due to associated mental health difficulties, problems with the associated pain that accompanies tics or the tics themselves being bothersome. It can also be due to a lack of awareness within the education setting, meaning that children are at times punished and asked to leave the classroom, meaning they miss out on valuable learning opportunities.

Social Impact

Tourette's is a widely misunderstood and stereotyped neurological condition historically associated with or defined by obscene language and socially inappropriate behaviour. Although it is true that 'coprolalia' (the clinical term for involuntary obscene language), 'copropraxia' (the clinical term for involuntary obscene gestures) and 'coprographia' (the

clinical term for the involuntary writing of obscene words) are symptoms of TS, they do not affect everyone with the condition and are not criteria for diagnosis. However, those who experience these types of tics do find them very difficult tics to manage and often report feeling socially isolated due to them. Many have been asked to leave places of worship and venues such as the cinema, have been removed from classrooms or social settings and some have been attacked as a consequence of their tics and others fired from jobs. People with TS report that their tics can often cause embarrassment, great pain, injury and physical disability depending on their severity.

Characteristically, tics vary in frequency and intensity over time (known as waxing and waning). In periods of increased tics, individuals can have reduced leisure participation because the tics often require all their physical and mental energy, leaving little room for anything else.

Adults with TS and employment impact

Tourette's affects individuals across their lifespan, it affects their ability to navigate life in a neurotypical world, particularly during their education years and into employment. Transitioning from childhood to adulthood can also be a challenging time, be that looking for employment or going to university. Living independently for the first time, managing finances, developing new relationships with peers / colleagues and juggling workload pressures can all be difficult for those with TS, often requiring significantly more intervention, nurturing and guidance from employers, family, and friends.

Wider health impact

Research shows that those with Tourette's are also 4 times more likely to die by suicide in adulthood compared to the public at large (reference: Fernández de la Cruz L, Rydell M, Runeson B, Brander G, Rück C, D'Onofrio BM, Larsson H, Lichtenstein P, Mataix-Cols D. Suicide in Tourette's and Chronic Tic Disorders. Biol Psychiatry. 2017 Jul 15;82(2):111-118. doi: 10.1016/j.biopsych.2016.08.023. Epub 2016 Aug 26. PMID: 27773353.).

Research hasn't been conducted into children and young people but we know from our service users that many of our young people have attempted suicide and sadly some young people from our community have taken their own lives and are no longer with us. The affect tics can have on the body in relation to pain, the feeling of embarrassment and social isolation that can come from having Tourette's and the lack of treatment being readily available to many in the community has a huge impact on individuals, both mentally and physically and some find this is their only way out.

Tourette's can affect an individual in the following ways:

- Pain – Tics can cause significant pain and tension which reduces overall quality of life and the ability to complete normal daily tasks. Motor tics can cause excessive wear on the body, many individuals often needing pain management and physiotherapy. Certain tics can be self-injurious in nature, causing pain, bruising, dislocation and sometimes broken bones
- Physical fatigue and exhaustion due to the tics themselves and also the suppression of tics
- Physical disability - Rarely, long-standing tics of the head and neck can result in damage to the spinal cord (myelopathy) causing weakness or paralysis and requiring neurosurgical rescue.
- Mentally – due to the prominence of tics to self and others, tics often have an impact on an individual's confidence, self-esteem and mental health which causes significant anxiety. This often causes problems with making friends and sustaining relationships and impacts an individual's ability to socialise and also their ability to gain and maintain employment. Increased anxiety leads to increased frequency and intensity of tics.
- Embarrassment – Due to prejudice and judgement from misconceptions and assumptions about the condition
- Sleep disruption – tics can affect the individual's ability to fall and stay asleep, which exacerbates fatigue, making them constantly physically and mentally exhausted
- The sensory environment can have a huge impact on tics. Noise, light, smells etc can often make tics increase which often then limits environments individuals may go to
- Mobility and independence can be affected by motor tics
- Communication difficulties - vocal tics can affect the flow of speech, both the ability to speak, and also the quality of speech can be affected
- Socially - especially when tics can be noticeable to others
- Academically - individuals often don't achieve their academic levels due to exclusion from the classroom or problems with focusing when in the classroom due to tic suppression
- There is an increased metabolic / cardiovascular risk and suicide risk associated with Tourette's

Access to Healthcare and its impact

In this study https://link.springer.com/article/10.1007/s10882-021-09829-2 adult participants with TS reported that General Practitioners had poor awareness of Tourette syndrome, a lack of clinical expertise and difficulty referring on to specialist services which resulted in patients having delays in receiving a diagnosis. The study also revealed the existence of TS stigma within the healthcare system. Half of the sample also described

experiencing discrimination from healthcare workers. This stigma, the lack of awareness about the condition and the lack of medical support for the condition has a huge impact on those with the condition and their families. The condition itself is extremely difficult to manage but when no medical support and interventions are available, it only further adds to the complexities.

A survey that was conducted by Tourettes Action in 2021 was completed by 1034 respondents

National findings:

- 56% of people who received a diagnosis waited longer than 1 year
- 29% of people who received a diagnosis waited more than 2 years
- 19% of people who received a diagnosis waited more than 3 years

52% said that they were diagnosed and then discharged at the same appointment and provided with NO ongoing care

North-West findings:

- 55% of people who received a diagnosis waited longer than 1 year
- 37% of people who received a diagnosis waited more than 2 years
- 28% of people who received a diagnosis waited more than 3 years

61% said that they were diagnosed and then discharged at the same appointment and provided with NO ongoing care

**2. How do symptoms and/or the condition or disease affect carers and family?**

Tourette's affects the whole family unit and is challenging for all. Parents and carers often have to adapt the way they parent their children with TS, which can have a detrimental impact on siblings. Tics can often be frightening and upsetting for siblings, especially in the early days of diagnosis. This can result in siblings not wanting to bring friends home which can lead to sibling isolation. Family groups or parents out in public with a child with TS face the same social isolation and negative and judgmental reactions from the general public that would be experienced by the child. An example would be parents being aggressively 'told off' by members of the public for not quieting a child with a shouting tic or judgemental stares and whispering when a child has a swearing tic and the parents do not react.

The nature of Tourette's means that the tics wax and wane (go up and down, come and go), often meaning that the support required is not always consistent over time. This in itself can cause issues as many have the notion that 'they were ok yesterday'. This leads to isolation for parents and the family as a whole as many do not understand or believe what is going on in the family unit, there is often an element of distrust from school, employers and friends and family.

Currently there is limited support available for people with TS, the ability to access treatment is a "postcode lottery". The lack of access to support means that parents are often desperate for support by the time they contact Tourettes Action as they have nowhere to turn to and the charity is the only place where they can seek more information and answers to their questions. Parents are unsure how to support their child who may well be in pain with their tics and struggling to access school fully. This can then have an effect on the parent's ability to work, socialise and sleep. As a result, family dynamics change and very often parents report mental health difficulties of their own.

Adults with TS tell us that the unpredictability of their tics can mean that they are not able to support with parenting duties or household tasks at short notice and that they may need to take rests at inconvenient times. They also often have to cancel plans at short notice. Sometimes their vocal tics can be hurtful and in context, which despite all the understanding in the world can hit a nerve with a loved one at the wrong moment. This obviously can have a negative effect on family relationships, be that with partners or children, and often brings shame and embarrassment.

Those with TS often face discrimination and stigma on a daily basis, which not only affects them individually but also affects the family unit, many often feeling helpless and unsure how to best support in these situations. It often leads to the social circle becoming smaller. Many families have been told to leave places of leisure and worship, children have been suspended and excluded from school and sporting activities and adults with TS have lost jobs as a result of their TS.

Finances can be affected as many families and carers report paying privately for treatment as NHS treatment is not readily available locally to them. These costs can often be ongoing, not just requiring assessment and diagnosis, but ongoing costs of privately

funding treatment such as Comprehensive behavioural intervention for tics (CBiT). Some families may be successful in securing treatment at one of the few national specialist clinics but these are often huge distances from an individual's home, often resulting in large travel and associated costs, although remote assessment and treatment has reduced travel and associated inconvenience. Stability in employment can also be an issue for adults with TS, which also has a negative consequence on family finances. This same issue also affects parents of children with Tourette's who report that they need more time off work to support their child. This can result in a reduction in working hours or resignation from jobs.

As TS symptoms can be unpredictable, this can mean that a planned activity/family day may have to be altered or cancelled at short notice. This then affects the whole family unit and can sometimes cause resentment between siblings.

Many report that they have limited contact with extended family members, as the members do not have the lived experience or daily contact with the individual with TS, so often respond inappropriately. This comes about because of a lack of understanding, with extended family often commenting on tics without thinking, despite knowing the individual has TS. Thus, family occasions i.e. Christmas / Easter / Birthdays are often limited to close family and friends only, further making their social circle smaller and isolating their family unit further.

Other ways in which families can be affected by TS:

- Prejudice and discrimination by society, shops and leisure venues often causing the family to feel socially excluded and unable to access everyday activities like going to the supermarket or the cinema.
- Many have experienced anger from strangers who have found tics inappropriate, this often makes the social circle smaller and further adds to the feeling of being excluded from society
- Break up of families due to extra pressures mentally, socially and financially
- Time is required to complete applications, attend medical appointments and support needs that could otherwise be spent on more everyday family activities and interactions
- Breakdown in relationships within the family unit, simple daily activities such as eating a family meal together can be affected, the tics can sometimes be frustrating when they are disruptive to other activities at home, such as trying to watch a TV

programme together, which often means that whole family activities can sometimes be limited

**3. Are there groups of people that have particular issues in managing their condition?**

There is a wide range of severity of Tourette syndrome and there are common associations with other neurodevelopmental conditions which together affect educational and social outcomes. Many people with TS have co-occurring conditions, such as Attention Deficit Hyperactivity Disorder, (ADHD present in 54%), Autism Spectrum Disorder (ASD), Obsessive Compulsive Disorder (OCD present in 50%), Anxiety, Depression, Sensory Processing Differences and Functional Neurological Disorder (FND). People with co-occurring conditions often have the most difficulty managing the condition. 20% of people with Tourette Syndrome also have diagnosed ADHD and OCD.

Those also diagnosed with FND, ASD and Anxiety seem to have increased difficulty managing tic symptoms and often those diagnosed with co-occurring ADHD and OCD have increased difficulty managing psychological stressors which in turn exacerbate their tics.

Pain, irritability, poor focus, sensory differences, co-occurring mental health diagnosis all feed into tics, and often increase their severity and frequency but more importantly can reduce the persons emotional and physical capacity to tolerate the challenges of daily life and to live with the pain and distraction that tics often cause.

TS affects all communities equally but those who live in areas of the country where there are no TS services in place (meaning that support isn't readily available to them) are likely to be more disadvantaged. This likely means that these children and young people and their families struggle more with their symptoms and find it harder to manage and cope. When services are not available locally, individuals are rarely able to access relevant services in other areas of the country as referrals are usually based on local services delivering follow up care. This means that families very often have to resort to paying for a private assessment and treatment if they are to receive care.

New emerging research is suggesting that there is a difference in symptom trajectory for males and females. Females are often diagnosed on average later than males and are less likely to see an improvement in their symptoms as they get older, their symptoms may in fact increase with age. An additional contributing factor is that females are under diagnosed with ADHD and ASD and it is often part of this diagnostic process that tics are picked up and diagnosed.

People with TS from an ethnic minority background are likely to experience unique problems around seeking a diagnosis. The condition impacts all from a diversity perspective yet there are less role models that are diverse. With the condition still being stigmatised people need to see people who look like them to encourage them to be their best self, this is often felt more by those who are diverse in more than one way.

Older adults with TS often struggle with symptoms, particularly in relation to pain management and damage to muscles, joints and can have an increased risk of falls.

## Experiences with currently available technologies

**4. How well do currently available technologies work?**

As far as we know, there is nothing currently in this space provided by the NHS as an established and available treatment that is specifically for tics.

There are prospects for new non-invasive brain stimulation treatments and delivery of evidence based behavioural treatments however they are currently severely restricted in access in the NHS due to the limited commissioning of traditional treatment services. It is however not clear whether online behavioural therapies reduce tic-associated urges, how effective online behaviour therapies are compared with group/individual in-person therapy, whether the therapies impact both motor and vocal tics and symptoms of co-occurring conditions and how effective the therapies are in relation to each other.

There are meditation apps that are promoted to those with TS, which can be helpful to relax when tics are not severe to prevent further tics. However, when tics are very present, the focus on bodily sensations can make them worse. Nuance is needed with guided relaxation tailored to TS and empirical studies will help to guide this.

**5. Are there groups of people that have particular issues using the currently available technologies?**

It is unclear if behavioural therapies are suitable for those with unmedicated ADHD. Individuals with processing issues and ADHD are reported to often struggle to engage in traditional therapeutic interventions so would also struggle with the technologies available.

Behavioural therapies require motivated parents and children/young people to practice the techniques.

Online therapies may not be accessible to all socio-economic groups.

Young children can find it hard to engage in traditional therapeutic interventions, often only being accessible for children over the age of 9, those younger can struggle to participate, although studies have shown effectiveness in children as young as 5 years of age, with high levels of support from carers / parents.

Some forms of behaviour or psychological intervention such as CBiT or Habit Reversal Therapy (HRT) need to be adapted where there is a specific intellectual or communication need, for example in those with ASD.

## About the medical technology being assessed

**6. For those <u>with</u> experience of this technology, what difference did it make to their lives?**

Comments made in this section were gathered from asking our service users to reflect on their experiences of participating in either the ORBIT or Neupulse trials. We had more feedback on some technologies than others, which is reflected in the length of comments. Although not technically technologies, we did receive feedback on ERP, which we have also summarised.

There is existing evidence from clinical trial participants of potential useful therapeutic benefit on tics. If tics reduce you might expect this to improve quality of life in those patients where their tics had been reducing their quality of life.

<u>Neupulse wearable wrist device:</u>

Many have reported that the device has had a huge positive effect. They have expressed how this is life changing for them in terms of their pain, their anxiety and their ability to

relax in social settings. It has reduced tics and improved safety and social mobility at the click of a button.

Service user quote: *"It worked for my child. I watched them throughout and they visibly relaxed. At the end, they were slouched back in their chair and fiddling with their hair- I had never seen them so relaxed."*

Not all comments have been positive, some members have reported that the device felt uncomfortable for them and they decided not to continue with the trial.

A point to note is that the Neupulse trial was for individuals 12 years of age and older whereas tics typically onset at about 5/6 years of age. Therefore, it is not known if younger children could tolerate the device. Comments we received were from individuals who took part in the trial and were of the age 12 and up.

Online Remote Behavioural Intervention for Tics (ORBIT) :

Parents reported that they found this life changing as it gave their child the knowledge, and confidence to know that they had the ability to control and manage their most troublesome tics in social situations, if they wished. For the person with TS, the key benefit was the knowledge that they had some control back over their body. It meant after being isolated and not leaving the house for months, being able to go back to school and engage in life outside the house again.

Service user quote *"It was a blind study and we had guessed very early on that we were in the group for psychoeducation. Overall, I feel he benefitted as he was at that age where psychoeducation was really important and it came at the right time for us as a family. I think the activities they asked him to do were quite immature at times but I guess that may have reflected their audience.*

*The visits to London, as parts of the trial, were tricky even though we only had to do this twice. Once at the beginning for a base line assessment and once at the end for a review. It was hard to keep occupied on the train as he had lots of OCD and anxiety on the train around people.*

*In terms of it having an effect on his life, this wasn't noticeable as he was already in a family with lots of knowledge of TS but the resources definitely helped echo what we were teaching him and I can see how this would have helped other families that perhaps were not as knowledgeable as us. I liked the fact that we had a direct person we could email at any time if we had any questions or issues with any of the weekly tasks. It was very well*

*organised. I wouldn't say that it had a direct impact on his symptoms as such, maybe a little improvement on his anxiety, which in turn may have lessened his tics slightly."*

Exposure and Response Prevention (ERP)

Individuals report that this can be useful for social adaptation at key moments for short periods of time (banks, airport security) but is mentally and physically exhausting and they often struggled with a rebound of uncontrollable tics later in the day.

**7. For those without experience of the technology being assessed, what are the expectations of using it?**

Neupulse wearable wrist device:

There is much excitement and anticipation in the TS community for the wearable wrist device. People are desperate for help managing symptoms and they have high expectations for this technology to be effective.

People with TS believe the device will reduce the social / functional impact of symptoms, applicable to all areas of life, e.g. social, work/occupation, daily living, caring responsibilities. They are hopeful it will aid their sleep, give a reduction in tics and severity of tics, enabling them to feel more in control of their actions and giving them a chance to manage their own condition, which would give them the ability to work, be educated and participate in normal daily activities without fear of stigma or judgement. These expectations need to be evaluated through empirical research and focus on metrics which go beyond tic frequency, including quality of life measurement, school attendance, mood etc.

Some members of the community have raised concerns that the device may be used by adults to "quiet the child down" not for the benefit of the child but for the benefit of others, such as in a school environment where disruption of the class due to tics may not be wanted. They feel that the device may not always be what the child wants but may be what the parent or teacher wants.

Online Remote Behavioural Intervention for Tics (ORBIT) :

Access to existing therapies (e.g. CBiT, HRT, EPR) nationwide is very limited, so members of the community are hopeful that this will enable all to access interventions, potentially

giving a reduction in the need for medications and any complications this may include, for example, side effects or interference with other neurological conditions.

There is some concern that digital therapy will be used, not because it is better, but because it is cheaper and possibly easier to deliver. There are already evidenced based treatment interventions, that are the current 'gold standard', such as CBiT and ERP however patients are not able to access these in many areas. Some people feel that what is really needed is better funding to allow access to these.

**8. Which groups of people might benefit most from this technology?**

Essentially anyone with TS who desires better symptom control stands to benefit from these technologies, if demonstrated to be effective. There are groups that are likely to benefit more, in particular due to external factors related to access to healthcare, or more intrinsic factors related to their own symptoms/presentation.

These include;

<u>People who currently have limited access to treatment</u>

Many in the UK are unable to access treatment following a diagnosis due to a lack of service provision. Having a digital therapy available to all would mean that the 'postcode lottery' would no longer exist and everyone would be able to access care regardless of where they lived in the UK. This however still relies heavily on individuals being able to access a diagnosis, which unfortunately for many can take years.

<u>Those having specific barriers in accessing face to face treatment</u>

Digital therapies also have the added benefit of being conducted in the individuals own home and surroundings, meaning those who are unable to travel also benefit. Parents / family members would need to take less time off work for appointments and those on low / restricted incomes would be more able to participate as there would be no associated travel costs although travel costs are typically reimbursed within the NHS for people on low and restricted incomes anyway.

Individuals who don't want to or who are unable to learn and practice behaviour therapies and want to be able to control their symptoms at the press of a button would benefit from the wearable device.

Those for whom current treatment have not been effective

Those for whom medications have been unsuccessful or still desire additional symptom controls

Those for whom medication has resulted in intolerable side effects.

It is possible that these technological options could be preferable to the risks of medication adverse effects and non-responsiveness for many children and adults.

The wearable device specifically may be beneficial to: individuals who don't want to or who are unable to learn and practice behaviour therapies and people with certain communication needs who may not be able to engage with tradition interventions such as CBiT.

Those for whom control is a priority

Some of our service user report having control over their treatment, the ability to choose when they engage with it is very important, some technologies such as the wearable device, offers this control which traditional treatment like medications do not.

Some of our service users also report that technologies will allow them to participate at a time convenient to them, they are not restricted by appointment timings, they are in control of when they use the technology.

## Additional information

**9. Please include any additional information you believe would be helpful in assessing the value of the medical technology (for example ethical or social issues, and/or socio-economic considerations)**

The idea of a one-off costed device which can be purchased and controlled by the service user, which can be turned on and off as needed would mean that people with Tourette's can have respite from symptoms as and when they need it.

In areas of the country where services and support are scarce, many often report feeling abandoned, therefore having therapy available to all regardless of postcode would help enormously.

Treatment is not always needed or wanted following a diagnosis. Often psychoeducation is enough and is a very important step in learning to live with and manage the condition. The psychoeducational elements of the ORBIT trial and a similar trial carried out in Sweden using the same device showed that children and young people benefited similarly in tic reduction whether they received psychoeducation or exposure with response prevention *digitally (reference: Andrén P, Holmsved M, Ringberg H, Wachtmeister V, Isomura K, Aspvall K, Lenhard F, Hall CL, Davies EB, Murphy T, Hollis C, Sampaio F, Feldman I, Bottai M, Serlachius E, Andersson E, Fernández de la Cruz L, Mataix-Cols D. Therapist-Supported Internet-Delivered Exposure and Response Prevention for Children and Adolescents With Tourette Syndrome: A Randomized Clinical Trial. JAMA Netw Open. 2022 Aug 1;5(8):e2225614. doi: 10.1001/jamanetworkopen.2022.25614. PMID: 35969401; PMCID: PMC9379743.)*

Any digital therapies recommended should not be given to all who receive a diagnosis and should be as a supplement and following psychoeducation and only offered if needed or wanted. Consideration needs to be given to how the treatments presented to patients, particularly children in the context of social stigma. For example, is it disability positive? There is a balance to communicate the benefits of managing a symptom to help better an individual's life, and the less helpful message of investing disproportionate effort in repressing tics to avoid other people being uncomfortable.

Whilst this recommendation is specifically concerning children and young people (CYP), we also want to highlight that Tourette's is a lifelong condition and whilst CYP struggle to access treatment, this is also true for adults who also suffer from service neglect with no single service taking ownership of their care. Adults with TS are often also dealing with secondary disabilities as a result of their TS, very often caused by the repetitive nature and pain of the tics throughout their life, so would benefit hugely from any intervention offered.

The technologies need to take into account the high levels of co-occurring neurological conditions. For instance, how should someone with ADHD and TS use the behavioural programme, potentially at the same time as other online behavioural programmes for ADHD?

# National Institute for Health and Care Excellence
## Patient Organisation Submissions for Medical Technologies - Submission Template

Will data and outcome scores be communicated with the patient's clinical team? Will this be automated and interoperable? If not, how will outcome measures be reported through healthcare providers and administrative data for impact evaluation?

### Key messages

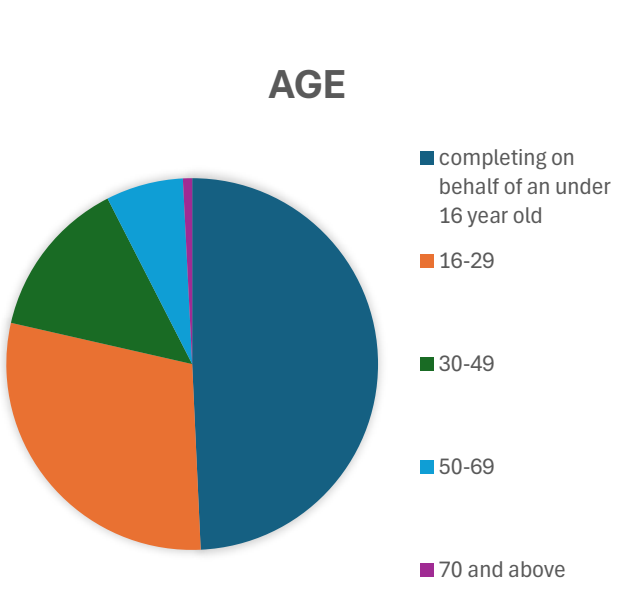
- **In up to five statements, please list the most important points of your submission.**
- The NHS currently has no pathway for a TS assessment and diagnosis and accessing support can take many years. As there is currently no set pathway in place, technology would be a stepping stone to this, defining what a treatment pathway 'could' look like. This alone won't fix the problem unless people have access to a timely diagnosis, thus full clinical guidelines and fully resourced services are needed for full benefit to be achieved.
- There are huge regional variations in care – It is imperative that everyone regardless of their location, financial or social status is able to access assessment, support and treatment
- The impact of tics and TS can have a huge life-long impact on people's ability to lead a normal life due to pain, stigma, isolation and anxiety, affecting education, employment and both physical, emotional and mental health
- TS causes an adverse impact on family life, i.e. parental employment, family finances, socialisation, sibling and family isolation and dysfunctional family dynamics
- The impact of additional needs and co-occurring conditions on the mental and physical wellbeing of people with TS across the lifespan needs to be considered

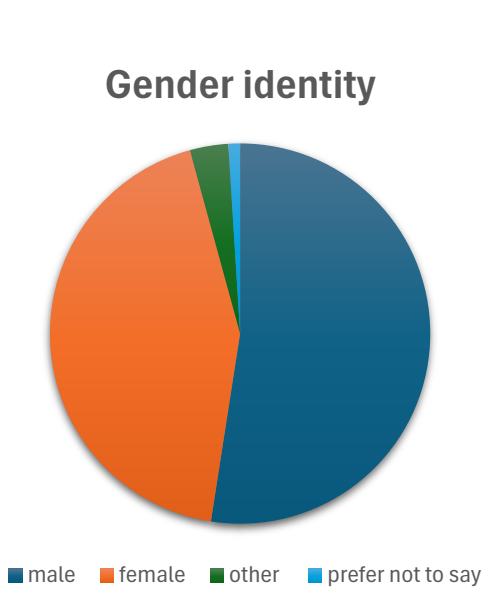
**Thank you for your time. Please return your completed submission to helen.crosbie@nice.org.uk and medtech@nice.org.uk**

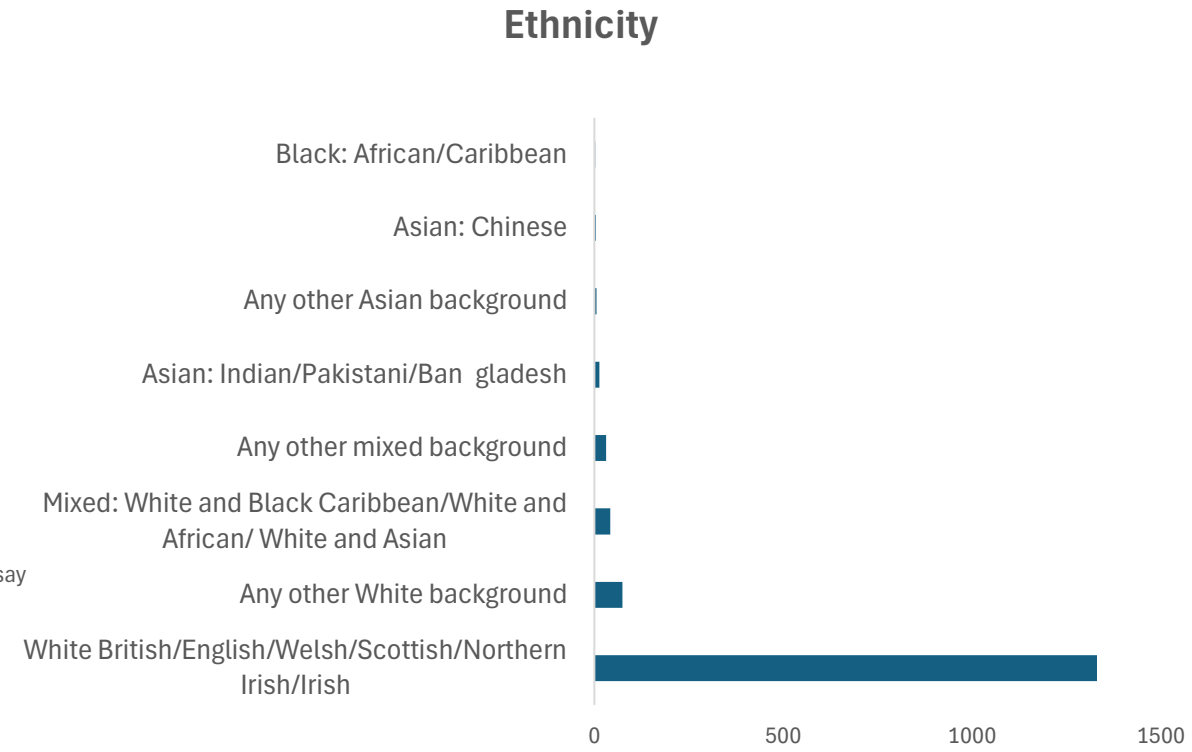
**Using your personal information:** The personal data submitted on this form will be used by the National Institute for Health and Care Excellence for work on Medical Technologies (including reviews) and will be held on the Institute's databases for future reference in line with our privacy notice.

# Patient survey

We have received a total 1508 responses to the patient questionnaire for Tic disorders and Tourette syndrome.  Following are the characteristics of respondents.

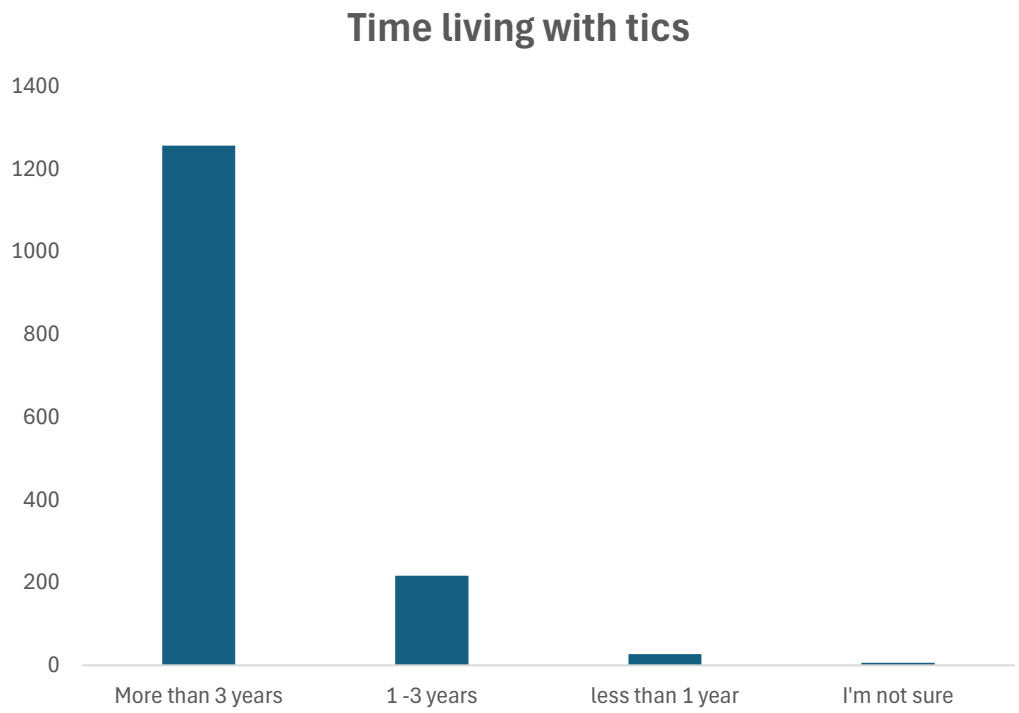


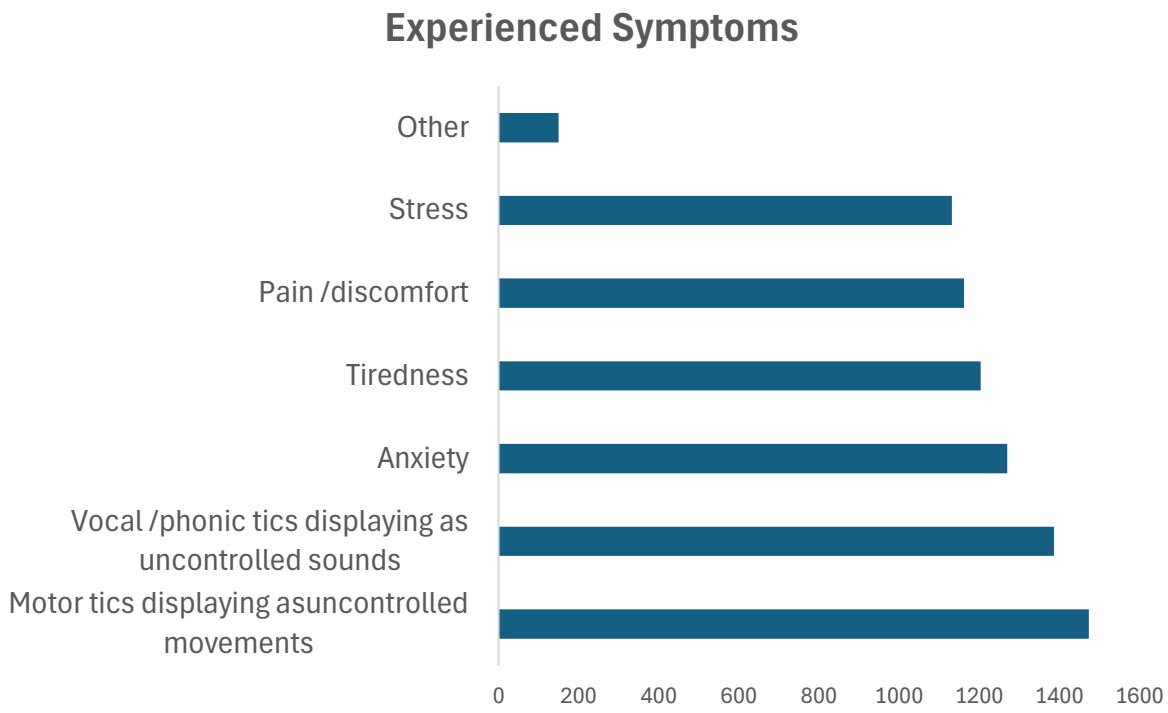




NICE

# History and symptoms




NICE

# Symptoms

**Motor tics:**

- Simple motor tics are repetitive movements involving a single muscle group, such as eye blinking, facial grimacing, shoulder shrugging & neck jerking.
- Complex motor tics are coordinated, purposeful-looking movements involving multiple muscle groups including jumping, kicking, touching objects or people, self-injurious actions (like hitting oneself), & gestures.

**Vocal tics:**

- Simple vocal tics include grunting, coughing, throat clearing, sniffing & barking.
- Complex vocal tics include repeating words or phrases, saying inappropriate words (coprolalia), or repeating what others say (echolalia).

**Mental tics:**

- Sometimes referred to as intrusive thoughts or mental compulsions
- Repetitive, involuntary thoughts, urges, or mental images that can feel similar to physical tics but occur internally within the mind.

**NICE**

"My daughter has been living with motor and vocal tics for around 10 years. When the motor tics first presented over 10 years ago, it looked like an electric current travelling through her whole body. She has experienced coprolalia which has been very awkward whilst out in public."

"I also have a jaw clenching tic which sometimes scares me into thinking I've accidentally dislocated my jaw. Another motor tic is punching the air randomly."

"(Vocal tics) change with time,words frases and sounds. Squeaks and squealing sounds when exited gulping air."

'My vocal tics have different voices. As if their different person the Tourettes uses."

"Vocally, my most frequent tic is a large screeching/screaming sound (that threatens the eardrums of anyone present)."

# Symptoms

## Physical Symptoms

- Pain and discomfort e.g. muscle pain & self-injury.
- Severe fatigue from tics, supressing tics and sleep interruptions.
- Prolonged paralysis during ‘tic attacks’.
- Loss of control over own body affecting walking, vision, balance & co-ordination.
- Negatively impacts on daily activities, ability to complete tasks & concentration.
- Difficulty communicating - completing sentences, loss of use of hands and ability to write/type.

## Behavioural Symptoms

- Tic disorders can include a range of behavioural manifestations that significantly impact an individual's life including obsessive-compulsive disorder (OCD), attention-deficit/hyperactivity disorder(ADHD), oppositional defiant disorder (ODD),learning difficulties, sleep disorders, eating disorders

“When my brother tics or my Mum mentions them or I hear the word tourette's or tics I can sometimes have a tic attack that I have to wait to pass.”

“My worst tic is my eyes blinking, particularly when I'm outside. It affects my balance when walking, its like walking blind. My eyes get very sore and can cause headaches. I was diagnosed when I was 28 years old and am now 71.”

“Low self esteem and self consciousness. Feeling like an alien.”

“nightmares sleep disorder Food avoiding.”

“My tics change over time so new parts of my body become painful whilst some tics leave lasting pain with tendinitis.”

# Emotion and social impact

| Emotion impact | Social impact |
| --- | --- |
| • Fear of leaving house or agoraphobia<br>• Low self-esteem & isolation<br>• Anxiety & depression<br>• Stress & excitement worsens tics<br>• Emotionally draining trying to supress tics<br>• Frustration, rage/anger outbursts, guilt | • Social withdrawal due to embarrassment, bullying & negative reactions<br>• Difficulty forming and maintaining relationships<br>• Education & work - significantly impacts attendance and ability for individuals to achieve in these areas, including sports & exercise<br>• Significant caregiver burden on families |

"My son was diagnosed with Tourettes when he was 13 had symptoms before that. He is 33 now and still lives at home (so his social life is minimal) as he would be unable to do most daily tasks."

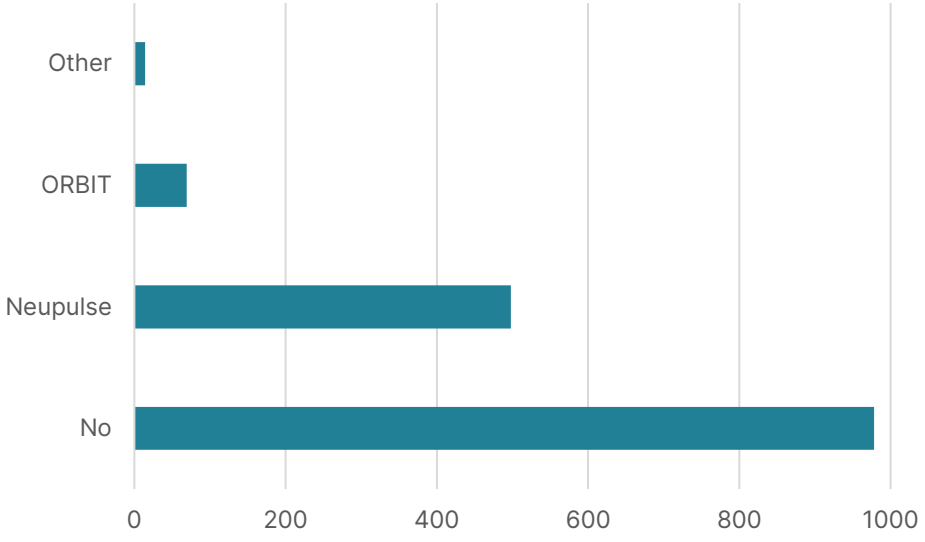
"anxiety relating to people noticing my tics or commenting on them (ableism, jokes, staring) loss of use of hands and ability to write/type, particularly affecting education."

"Depression, suicidal thoughts. Felt like there was no point to life and feeling not good enough despite being very loved, popular, smart and funny."

Whilst very intelligent feel have not been able to hold down a good.job, whilst
employers claim to be accepting to disabilities I know I have lost jobs because of TS. Emotionally it effects all relationships too

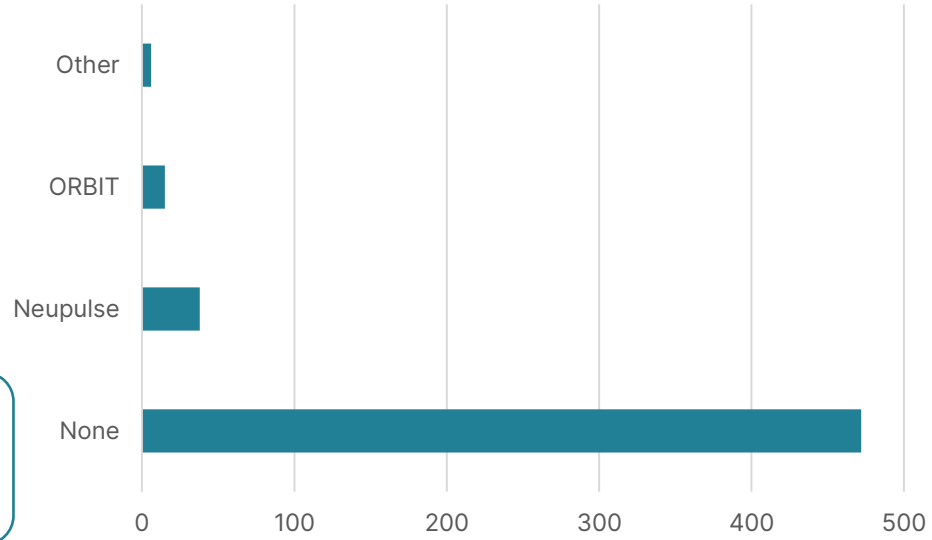
# Health technologies used for tics

Have you heard of any of these technologies used in tic disorders?




N.B.: Neupulse has only been used as part of a clinical trial

Which, if any, of these digitally enabled health technologies have you used for tics?




Please list the other digitally enabled technologies that you are aware of

Calm palm, TENS machine/watch, deep brain stimulation

Please list the other digitally enabled technologies that you have used

Calm palm, private treatment, TENS machine/watch

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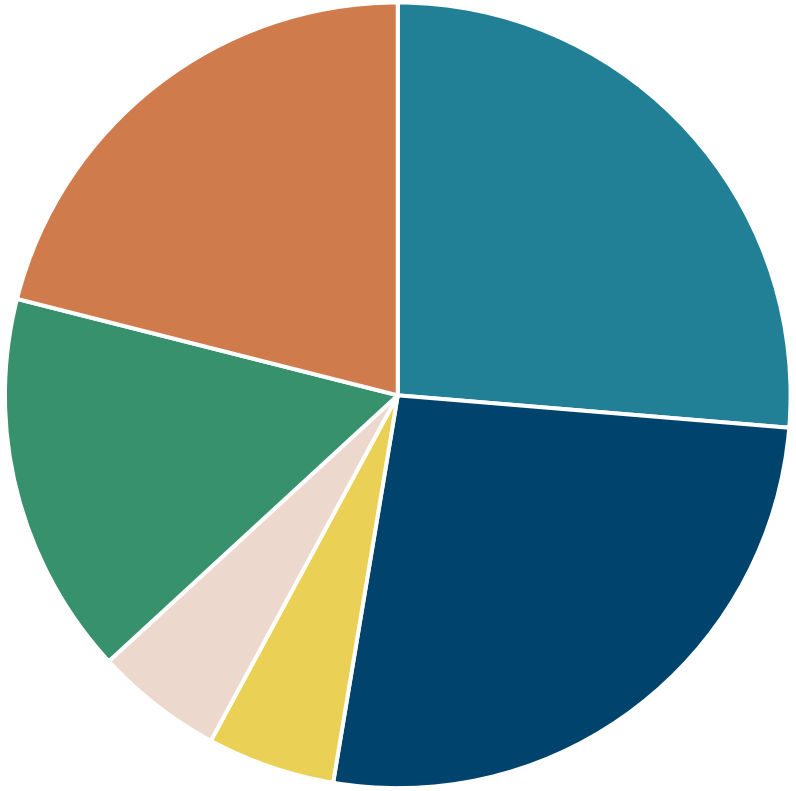
# Health technologies used for tics - ORBIT

How did your experience of using ORBIT affect your tics?

"I would recommend it"

"helped him realise he wasn't the only person with tics"

"I enjoyed the tasks and my tics reduced slightly, but only for a short amount of time"




"Fully understood the condition, family could understand better how the condition effects the individual"

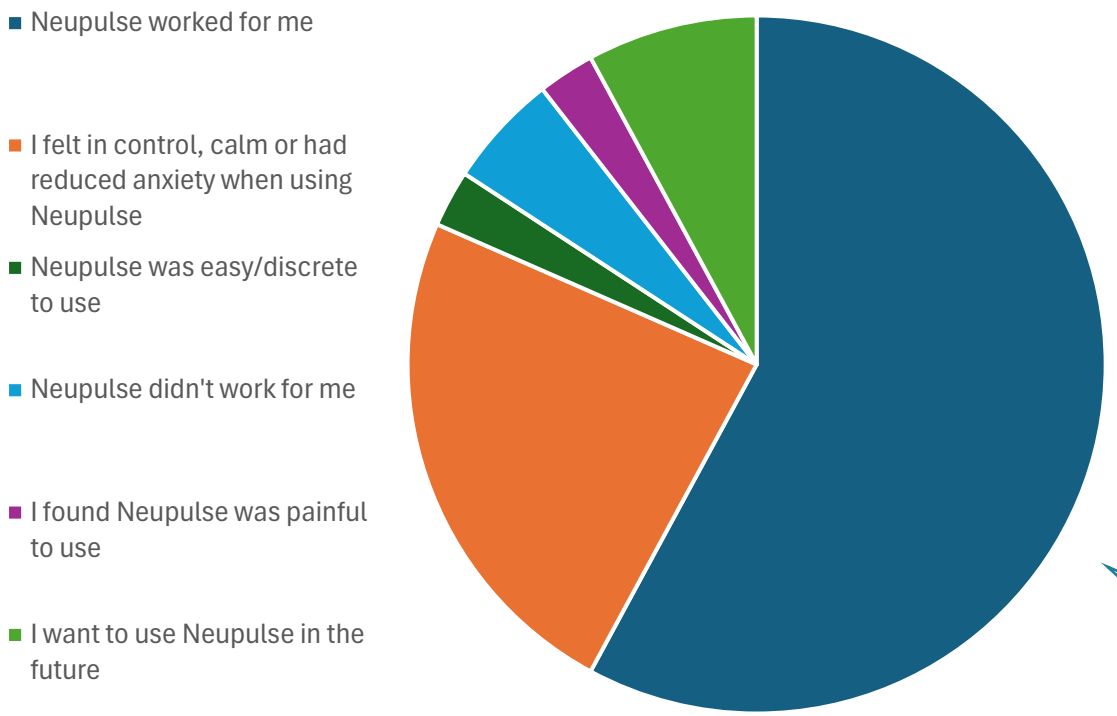
"As no specialists available it was my only avenue for education on tourettes and only available treatment"

NICE

# Health technologies used for tics - Neupulse

How did your experience of using Neupulse affect your tics?

N.B.: Neupulse has only been used as part of a clinical trial and some of the responders may have been in the control arm, using a sham device




"Found this very helpful at reducing my tics and especially helpful for anxiety"

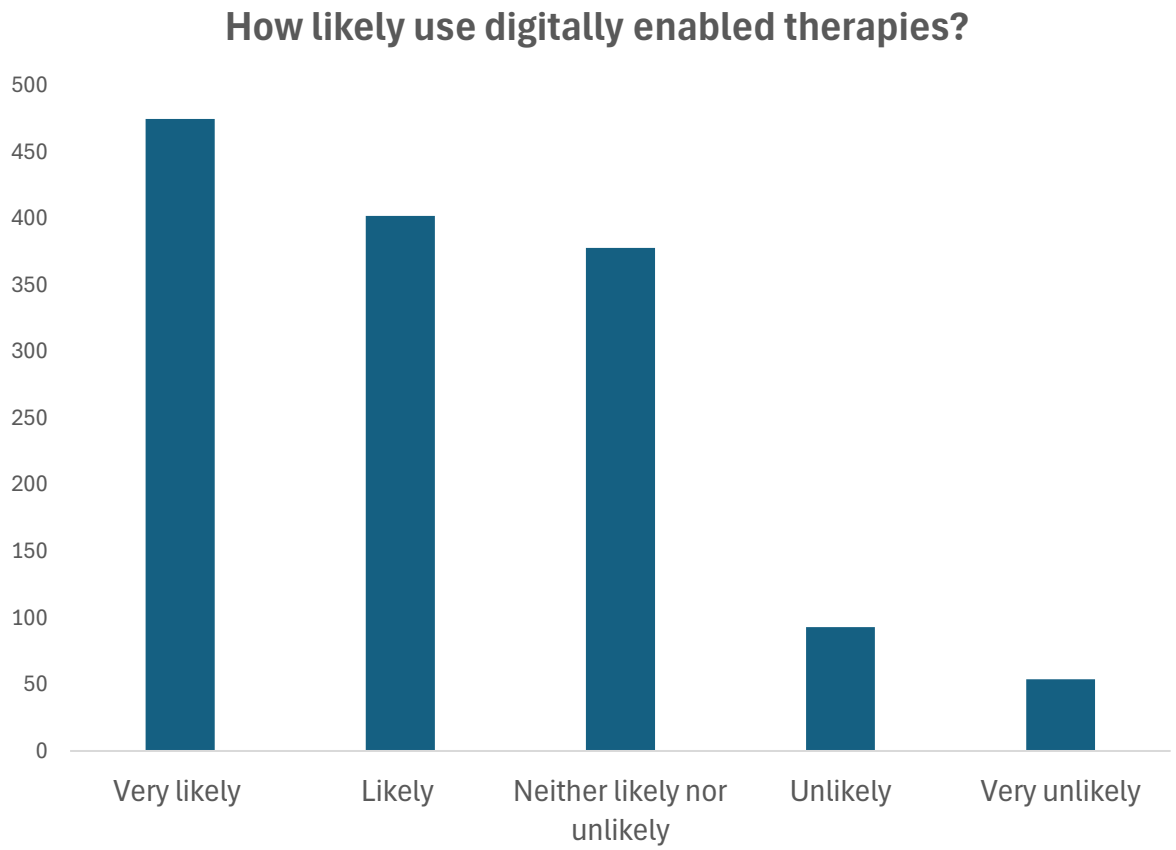
"I had a constant feeling of calmness throughout my body with no unwanted side effects"

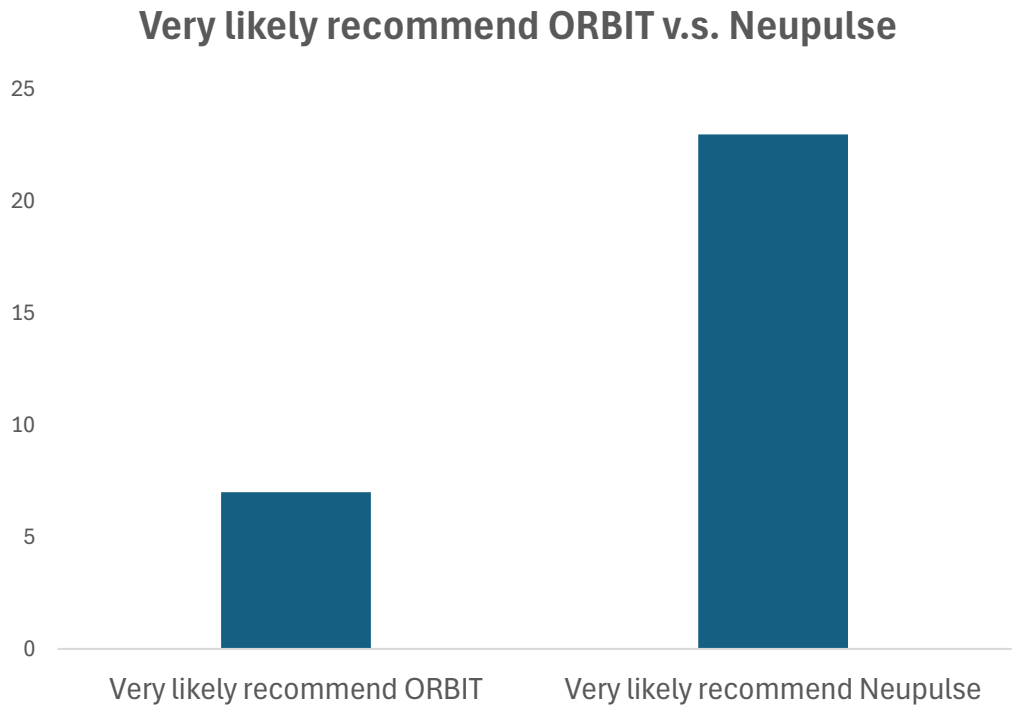
"I found it easy to wear and it wasn't noticeable by others"

"Neupulse digital technologies has helped me managed my tics in a non invasive way"

NICE

# Acceptance of using digitally enabled therapies

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# Acceptance of using digitally enabled technologies

| Reasons for the answer | | |
|---|---|---|
| Very likely & likely | Neither likely nor unlikely | Unlikely & Very unlikely |
| • Would like to try anything that helps with tics<br>• Would like try it due to its flexibility of use and less side effects compared to medication<br>• Would like to try Neupulse | • Need more information<br>• Worry about the cost and accessibility<br>• Would consider it if it's suggested by a medical professional | • Not sure it will work<br>• The child is too young to use digital technologies<br>• Tics has been well-managed so no need for digital technologies<br>• Don't like digital technologies<br>• Learning difficulties |

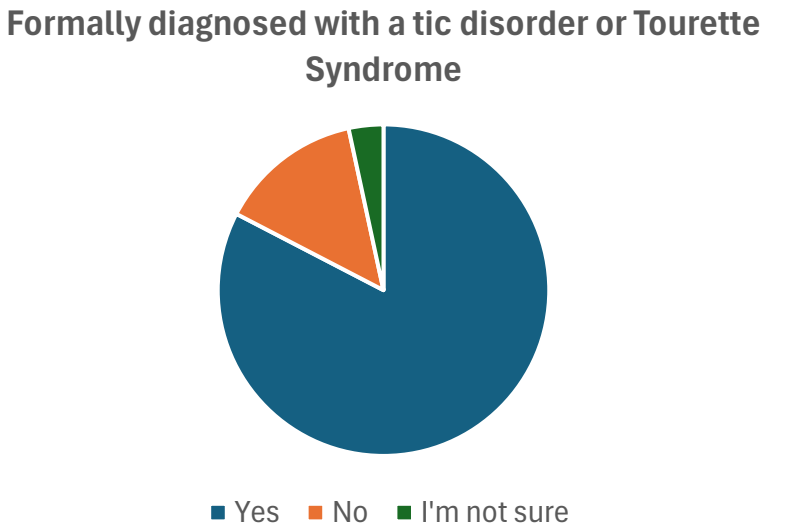
Anything that can help manage my tics would be amazing!

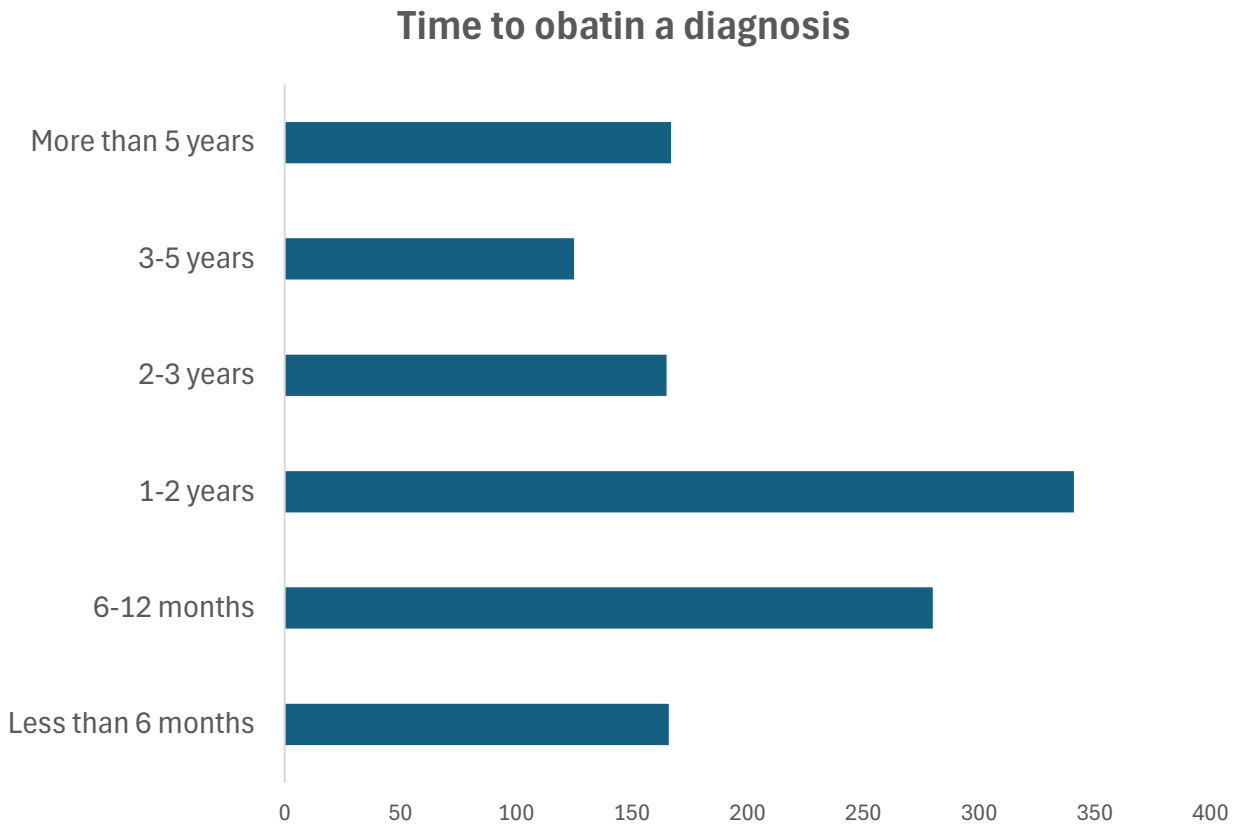
I will try anything to fix it. Only barrier is availability on the market and price

I would need to understand the nature and expected outcomes of the technologies before I would try them

Son has just turned 6 so unsure as to how able he is to engage with an online digital service rather than face to face

# Diagnosis

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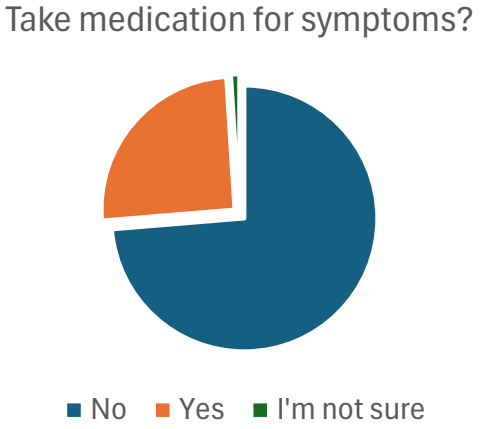
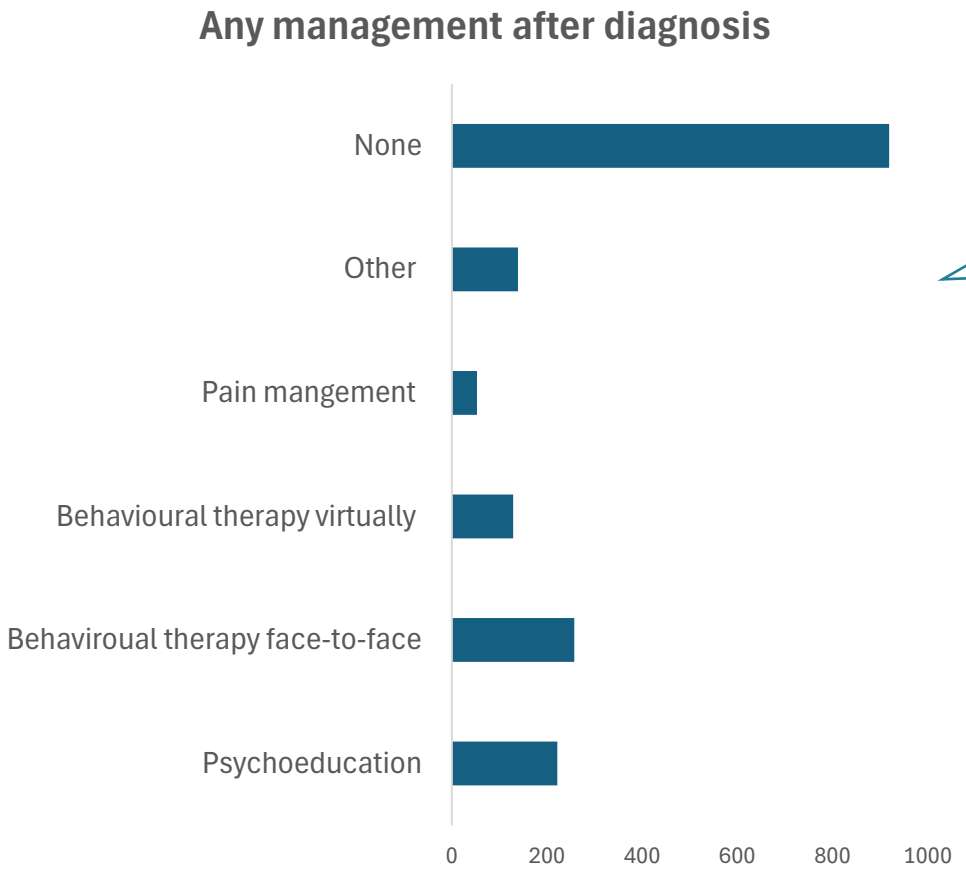
# Treatments




We were told we could be referred privately (diagnosis was private due to over 12 months wait nhs) and cost was too high

Not mature enough to have the behavioural therapy. Not want to go down the medication route

My son was referred to camhs, we received a phonecall from them but haven't even had an initial meeting with them in nearly two years. We went private for a diagnosis as the nhs couldn't/wouldn't help

NICE

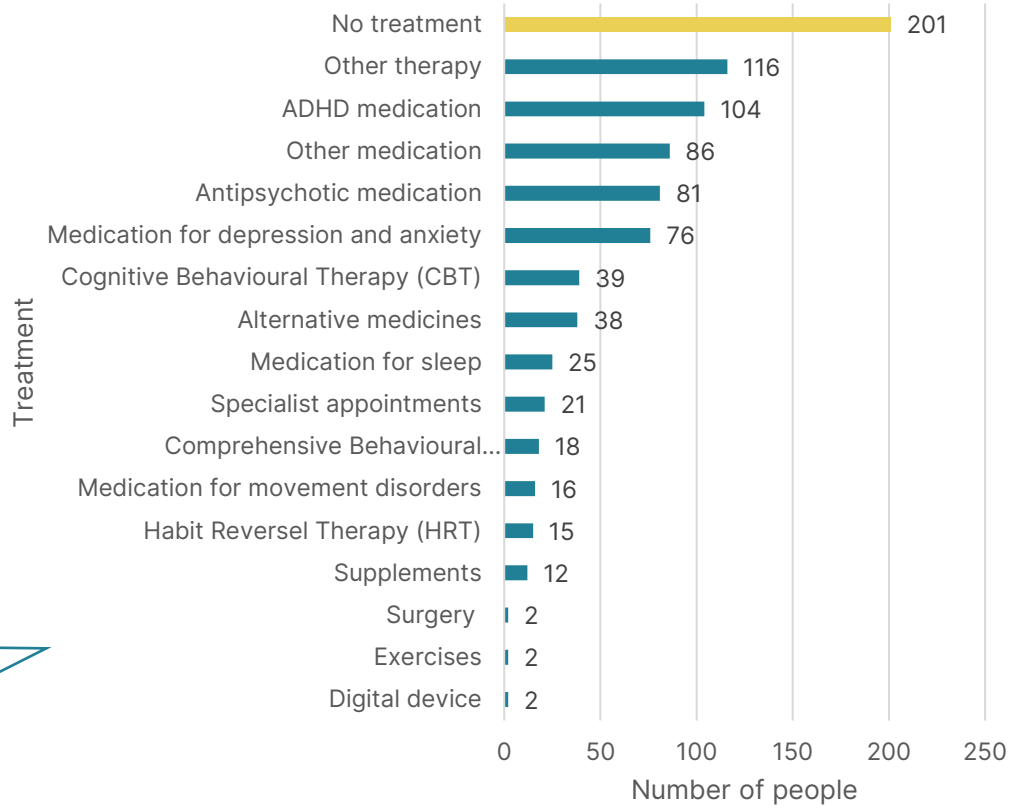
# Other treatments

Offered no treatment as told she's too young at 9 and just has to live with it for now. Absolutely disgusted

Guanfacine means our daughter can manage about one or two three-hour shifts of admin work per week. Without it, she has severe breathing problems.

Absolutely nothing and no support

**Treatment offered or received by those with tics (n= 767)**




Used to take medication but the side effects were too severe. Was told to try CBT but this did not help as no therapist was familiar with Tourette Syndrome

Everything we received we had to fight for. Pediatric assistance, Occupational therapy, psychological therapy.

Clinicians agree he has Tics Tourette but the pathway to diagnosis is slow. A recent addition of ADHD diagnosis concluded Tics Tourettes. Waiting for formal diagnosis

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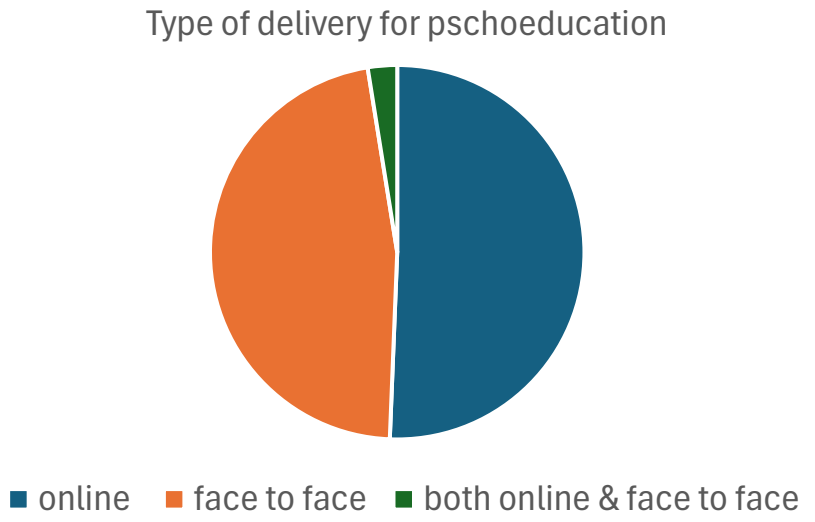
# Access to psychoeducation

79/195 respondents who had access to psychoeducation specified the type of delivery for psychoeducation. (online or face-to-face or both)

They usually had psychoeducation in a clinical setting including CAMHS, GOSH, NHS hospital clinics, private clinics and school.

The referral to psychoeducation is mainly from GP and specialist. A few are referred by the school and family members.




"I had to pay privately for it as GP was unable to help me"

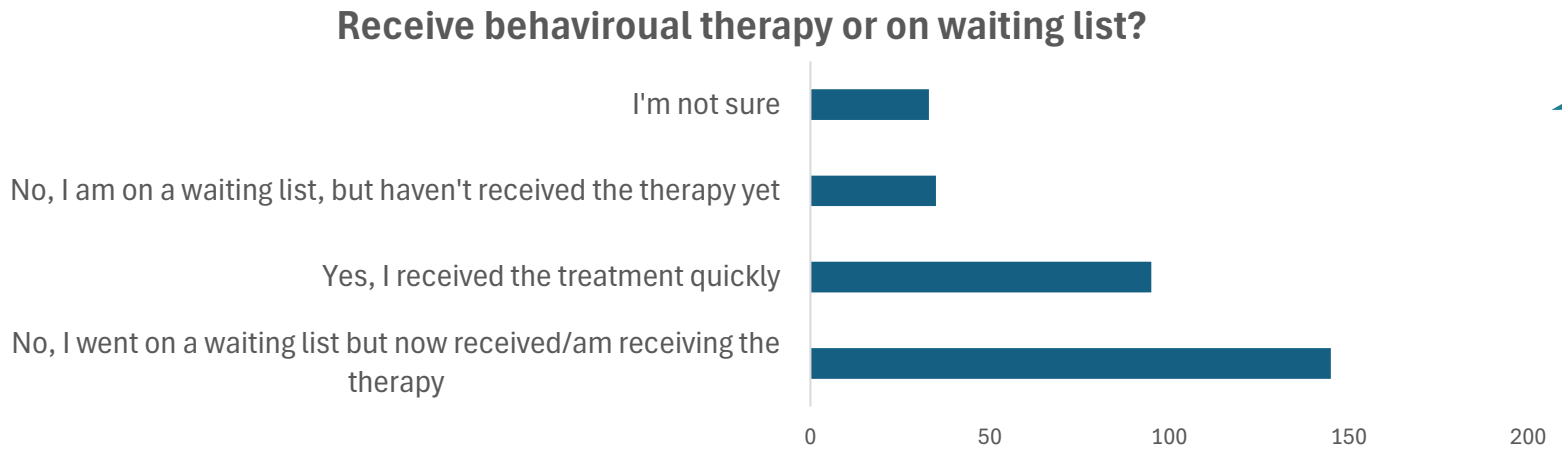
"Hospital, but appointment always cancelled not consistent and so its ineffective"

"gp referred to great ormond who provided group virtual psycho education to manage and understand tics"



CAMHS: Child and Adolescent Mental Health Services GOSH: Great Ormond Street Hospital

# Waiting for Behavioural therapy




98 respondents specified how long they've waited for behavioural therapy.


"Several months wait, after a couple of years waiting for diagnosis"

"Can't remember how long we waited. And NOTHING whilst waiting"

"I had to go through a complex process to secure funding for CBT it involved being assessed by lots of non-specialist clinicians and having to build evidence and advocate for myself strongly"

NICE

# Digitally enabled therapy for chronic tic disorders and Tourette Syndrome

**Produced by** Aberdeen Health Technology Assessment Group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**Date completed** **26 July 2024**
**Version** **1.1**
**Contains** [redacted]

**Source of funding:** This report was commissioned by the NIHR Systematic Reviews Programme as project number **136022.**

**Keywords:** Tic disorders, Tourette Syndrome, behavioral therapy, neuromodulation.

**Declared competing interests of the authors:** Miriam Brazzelli participates on the NIHR HTA Commissioning Committee 2023-2028.

**Rider on responsibility for report**

This report presents independent research commissioned by the National Institute for Health and Care Research (NIHR). The views and opinions expressed in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NICE or the Department of Health and Social Care.

**This report should be referenced as follows:** Boyers D, Cruickshank M, Mohammad A, Manson P, Swallow D, Counsell C, Brazzelli M. Digitally enabled therapy for chronic tic disorders and Tourette Syndrome. Health Technology Assessment, XXX.

**Contribution of authors**

Dwayne Boyers (Senior Health Economist) reviewed the identified cost-effectiveness evidence, supervised development of the economic model, conducted cost-effectiveness analyses, and interpreted their results.

Moira Cruickshank (Research Fellow) selected relevant papers from the literature, performed data extraction and risk-of-bias assessment of all studies included in the review of clinical effectiveness evidence, conducted statistical analyses, and summarised results.

Mohammad Azharuddin (Research Fellow) developed the economic model, contributed to the acquisition of input data for the economic model and to conducting cost-effectiveness analyses under the supervision of Dwayne Boyers (Senior Health Economist).

Paul Manson (Information Specialist) developed and ran the literature searches, retrieved full-text copies of the selected papers, and provided information support throughout the project.

Carl Counsell (Clinical Reader - Neurology) and Diane Swallow (Senior Clinical Lecturer - Neurology) provided expert advice and guidance on the clinical aspects of this assessment.
Miriam Brazzelli (Professor of Health Services Research) planned the systematic review of the clinical evidence, contributed to data extraction and quality assessment of identified studies, checked statistical analyses, interpreted results and coordinated all aspects of this assessment. All authors contributed to the writing of this report.

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**List of abbreviations**

| | |
|---|---|
| ADHD | Attention deficit hyperactivity disorder |
| AE | Adverse event |
| ASD | Autism spectrum disorder |
| BIP | Barninternetprojektet (Child Internet Project; Swedish digital platform) |
| C&A-GTS-QOL | Child and adolescent Gilles de la Tourette quality of life scale |
| CAP | Clonidine adhesive patch |
| CBIT | Comprehensive behavioural intervention for tics |
| CEAC | Cost-effectiveness acceptability curves |
| CGAS | Children's Global Assessment Scale |
| CGI-I | Clinical Global Impressions – Improvement Scale |
| CGI-S | Clinical Global Impressions Severity Scale |
| CHU9D | Child health utility nine dimensions |
| CI | Confidence interval |
| CTD | Chronic tic disorder |
| CYPMHS | Children and Young People's Mental Health Services |
| DAWBA | Development and wellbeing assessment |
| DBS | Deep brain stimulation |
| EAG | External assessment group |
| EQ-5D | EuroQol five dimensions |
| ERP | Exposure with response prevention |
| HCP | Healthcare professional |
| HRT | Habit reversal training |
| HSUV | Health state utility values |
| ICER | Incremental cost effectiveness ratio |
| iiPAS | Internet intervention patient adherence scale |
| MNS | Median nerve stimulation |
| NHS | (UK) National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NMB | Net monetary benefit |
| OCD | Obsessive compulsive disorder |
| ORBIT | Online Remote Behavioural Treatment for Tics |

| | |
|---|---|
| PSA | Propensity score analysis |
| PSS | Personal social services |
| PSSRU | Personal social services research unit |
| PTQ | Parent tic questionnaire |
| QALY | Quality adjusted life year |
| RCT | Randomised controlled trial |
| SD | Standard deviation |
| SE | Standard error |
| TENS | Transcutaneous electrical nerve stimulation |
| TS | Tourette Syndrome |
| YGTSS | Yale Global Tic Severity Scale |
| YGTSS-TTSS | Yale Global Tic Severity Scale – Total Tic Severity Score |

# Abstract

## Background

Persistent or chronic tic disorders and Tourette syndrome typically present around age 5 with severity peaking between age 10 and 12. Current practice varies between countries and depending on service availability. Treatment options include psychoeducation, behavioural therapy, pharmacological therapy, and deep brain stimulation. Digitally enabled interventions may help improve patient outcomes.

## Objectives

We evaluate the clinical and cost-effectiveness of digitally enabled technologies (ORBIT and Neupulse) and to identify evidence gaps for future research.

## Methods

Comprehensive searches of major electronic databases including MEDLINE, Embase, Cochrane Library, Web of Science, and CINAHL were conducted to identify relevant reports of published clinical and cost-effectiveness studies. Study characteristics and results were data extracted and assessed for risk of bias using the Cochrane risk of bias tool version 2. Where appropriate, data were pooled using random-effects meta-analyses. A Markov cohort model, based on 5 tic severity states, defined using the YGTSS-TTSS scale, was built to determine cost-effectiveness from a UK NHS perspective. Model inputs were obtained from the ORBIT study, through companies, and supplemented with clinical expert opinion and supplementary literature review.

## Results

Three trials reported in 14 publications were included. Two studies compared ORBIT with online psychoeducation, and one compared Neupulse active stimulation vs sham stimulation and a waitlist control. All three studies were assessed as low risk of bias. Meta-analyses pooled results across two ORBIT studies (445 participants in total). At 3- and 12-months, YGTSS-TTSS score was significantly lower for ORBIT compared to online psychoeducation, but there were mixed results for other secondary outcomes. Neupulse had statistically significant lower YGTSS-TTSS scores, and improvements in motor and phonic tic scores at 4 weeks compared to sham stimulation, but there were no differences for the YGTSS-Impairment score or the PUTS-R.

It was not possible to determine a definitive base case ICER due to a lack of long-term follow up data and uncertainty about the long-term combinations of effectiveness and intervention cost that might be seen in UK NHS practice. Probabilistic ICERs ranged from £642 per QALY gained to ORBIT being dominated. The probability of ORBIT being cost-effective at a threshold value of £20,000 per QALY ranged from 52% to 89% across a range of scenarios explored. Cost-effectiveness results for Neupulse were even more uncertain due to a lack of published data, only 4-week follow up, and uncertainty surrounding the intervention cost.

**Limitations**

There was limited evidence available for the technologies of interest and inconsistencies in the outcomes assessed. Comparators did not include face-to-face behavioural therapy and it was not possible to differentiate the effects of online delivery from those of ERP. Cost-effectiveness results should be interpreted cautiously due to a lack of long-term evidence.

**Conclusions**

Both ORBIT and Neupulse appear to significantly reduce YGTSS-TTSS scores but there were no improvements in the YGTSS-Impairment scores and mixed results across other secondary outcomes, meaning it is unclear to what extent improvements in tic severity scores can translate to improvements in quality of life. Cost-effectiveness estimates were highly uncertain due to a lack of long-term evidence.

**Future studies**

Replication studies are required to confirm observed results. Longer follow-up is required to determine whether benefits can be sustained after intervention delivery and assess cost-effectiveness. Future studies should consider selection of primary outcomes that measure the impact of interventions on people's daily lives.

## Plain English Summary

Tic disorders involve fast, irregular, and repetitive muscle movements. Motor tics involve body movements such as blinking and grimacing. Vocal or phonic tics involve repetitive sounds such as grunting or sniffing. Tic disorders usually start around age five and are worst around ages 10 to 12. Tic disorders that last for 12 months or more are called chronic tic disorders. People with Tourette syndrome have multiple motor tics and at least one vocal tic.

In the UK, the main treatments for tic disorders include psychoeducation (giving information to encourage acceptance of the tic disorder), drug treatment, or behavioural therapy (training the person to recognise when a tic is looming and how to quell it). However, limited access to specially trained staff means there are long waiting times. Treatments that can be delivered remotely using digital technology may offer a solution. This work evaluates existing evidence for digitally enabled interventions with respect to clinical usefulness, cost and value for money.

We reviewed the current evidence and found two technologies (ORBIT and Neupulse), studied in three good quality clinical trials. ORBIT is an online remote behavioural intervention for tics. It was compared to online psychoeducation in two trials (one in the UK and the other in Sweden) in people aged 9 to 17. Neupulse is a wrist worn device that delivers mild electrical stimulation to reduce the frequency of tics. One UK study compared Neupulse stimulation with sham stimulation in people aged at least 12 years. At 3- and 12-months after initial treatment, the tic severity score was lower for ORBIT compared to online psychoeducation. Neupulse also reduced the tic severity score after 4 weeks. For both ORBIT and Neupulse, there was no pattern of improvements in other areas of people's lives.

When we looked at value for money, it was unclear whether these treatments would lead to long-term improvements in quality of life and the long-term costs were uncertain. Further, longer-term studies are needed to decide which technology (if any) offered the best value for money to the NHS.

## Scientific Summary

### Background

Tic disorders are neurodevelopmental conditions characterised by fast, irregular, and repetitive muscle movements that can manifest in any part of the body. Tics can affect body movements (known as motor tics) while involuntary repetitive sounds are known as vocal or phonic tics. Persistent or chronic tic disorders refer to single or multiple motor or vocal tics (but not both) that have persisted for more than 12 months since the first tic onset. Tourette syndrome refers to multiple motor tics and one or more vocal tics that have been present at the same time (but not necessarily concurrently) during the course of the disease and have persisted for more than 12 months since the first tic onset. The mean age of onset for tic disorders is around 5 years with severity typically worsening between 10 and 12 years of age and then improving through adolescence into early adulthood. People with chronic tic disorders commonly experience psychiatric comorbidities such as attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD). Tic disorders can vary in severity and impact various aspects of people's lives, contributing to a reduced quality of life. Current practice varies between countries and according to the availability of local services but, in general, treatment options for chronic tic disorders include psychoeducation, behavioural therapy, pharmacological therapy, and deep brain stimulation. Digitally enabled interventions have the potential to improve access as well as equity of access to treatment for people with tic disorders.

### Objectives

The specific objectives of this assessment were to:

- Evaluate the safety and effectiveness of digitally enabled non-pharmacological therapy for treating chronic tic disorders and Tourette Syndrome in UK clinical practice (ORBIT and Neupulse);
- Develop an economic model to assess the cost-effectiveness of digitally enabled technologies for the non-pharmacological treatment of chronic tic disorders that are available or likely to become available in UK clinical practice.

## Methods

### *Clinical effectiveness*

Comprehensive searches of major electronic databases including MEDLINE, Embase, Cochrane Library, Web of Science, and CINAHL were conducted to identify relevant reports of published studies. Evidence was considered from RCTs and non-randomised comparative studies published in English and assessing the relevant digitally-enabled technologies. Data on the characteristics of the studies, participants intervention and comparator were extracted along with relevant patient-reported, clinical and intermediate outcomes, as well as information relating to the use of digital technologies. The risk of bias of included studies was assessed using the Cochrane risk of bias tool version 2. Where sufficient data were available and it was appropriate, data were pooled using random-effects meta-analyses.

### *Cost effectiveness*

A systematic literature search for all full economic evaluation studies of interventions for tic disorders in adults or children was conducted. A decision analysis, Markov cohort, model was developed, based on the ORBIT study, to assess the cost-effectiveness of ORBIT compared to online psychoeducation and Neupulse compared to a waiting list control. The model base case was run for a lifetime horizon and results reported as incremental cost per QALY gained from a UK NHS perspective. Costs and outcomes occurring beyond the first year were discounted at 3.5% per annum. Five health states were included in the model. Health states were defined according to quintiles of the YGTSS-TTSS score (very mild, mild, moderate, severe and very severe tics). Transition probabilities between health states were obtained up to 18 months from the ORBIT study and up to 4 weeks from unpublished data obtained through personal communication with the company for Neupulse. Given uncertainty surrounding the long-term outcomes of Neupulse, the EAG consider this comparison to be more in line with NICE's early value assessment approach. Intervention costs were obtained from the published literature and directly from companies. Health state costs and utilities were based on CHU-9D data reported within the ORBIT study. The model was fully probabilistic, and a range of scenario and probabilistic analyses were undertaken to explore uncertainty in the base case conclusions.

## Results

### *Nature, description and quality of the available evidence*

The database search identified 379 unique publications and three further reports were identified. Three trials reported in 14 publications were included in the review. Two studies compared ORBIT with psychoeducation (one in the UK and the other in Sweden) and one UK-based study Neupulse active stimulation with sham stimulation. The two ORBIT studies recruited people aged 9 to 17, and the Neupulse study recruited people aged at least 12 years. All three studies were assessed as being at low risk of bias according to the Cochrane risk of bias tool version 2.

### *Summary of benefits and risks*

We were able to combine results of two outcomes assessed at two time points across the two ORBIT studies (445 participants in total). Pooled results at 3- and 12-months for YGTSS-TTSS in the ORBIT studies showed statistically significantly lower scores for the intervention groups than the control groups. However, no significant improvements in tic-related impairment and distress measured using the impairment score of the YGTSS were observed between treatment groups. In each ORBIT study, secondary outcome measures did not show a consistently greater response in the ERP group compared to the psychoeducation group at all assessed time points. In the UK ORBIT study, CGI-I showed a greater response in the ERP group at 3, 12 and 18 months but not at 6 months. In the Swedish ORBIT study, CGI-S showed a difference in favour of the ERP group at 3 months, but not at 6 months. In both studies, the CGAS showed no differences between intervention groups at 3 months and a positive difference in favour of the ERP group at 12 and 18 months in the UK ORBIT study. The estimated mean difference in the Parent Tic Questionnaire favoured the ERP group in the UK ORBIT study at 3, 6 and 12 months but not at 18 months and was not significant at 3 and 12 months in the Swedish ORBIT study. Similarly, in the UK ORBIT study, other measures evaluating anxiety and mood, emotional, and behavioural functioning did not show a consistent pattern of response at all assessed time points. In general, participants' engagement with the interventions, adherence and dropouts were reported to be similar between intervention groups.

The Neupulse study reported statistically significant lower YGTSS-TTSS scores at 4 weeks in the active stimulation group compared to the sham stimulation group.

Greater reductions in YGTSS motor and phonic scores were also observed among participants receiving active stimulation than among those receiving sham stimulation. However, no significant differences between treatment groups were observed for the YGTSS-Impairment score or the PUTS-R.

***Summary of costs and cost-effectiveness***

It was not possible to determine a definitive base case ICER due to a lack of long-term follow up data and uncertainty about the long-term intervention costs that might be required to maintain, if possible, intervention effectiveness at the observed trial follow-up time points. For the comparison of ORBIT vs. online psychoeducation, transition probabilities were broadly similar in both groups, suggesting a lack of clear evidence of long-term benefit. This was reflected in substantial uncertainty surrounding the estimated ICERs. Probabilistic ICERs ranged from £642 per QALY gained to ORBIT being dominated. The probability of ORBIT being cost-effective at a threshold value of £20,000 per QALY ranged from 52% to 89% across a range of scenarios explored.

Cost-effectiveness results for Neupulse were highly uncertain due to a lack of published transition probability data, short 4-week follow up, and uncertainty surrounding the most likely intervention device and subscription costs if the device were rolled out to the UK NHS. Transition probabilities were based on small counts and longer follow-up is required to determine whether initially optimistic improvements can be sustained longer term.

**Conclusions**

Two studies comparing ORBIT with psychoeducation (one each in the UK and Sweden) and one UK study comparing active stimulation with sham stimulation showed that tic severity in terms of YGTSS-TTSS scores was lower in the intervention groups as compared to the comparator groups at follow-up periods ranging from 4 weeks to 12 months. No improvements in the YGTSS-Impairment scores were evident and secondary outcome measures showed a mixed response across time points and studies. The EAG do not consider it possible to make strong recommendations in favour, or against, either intervention given the current evidence base for cost-effectiveness.

***Strengths, limitations and uncertainties***

Thorough and robust methods were used for this assessment. However, there was limited evidence available for the technologies of interest and inconsistencies in the outcomes assessed and their timing and further meaningful analyses were hampered. The comparators of the included studies did not include face-to-face behavioural therapy and it is not possible to differentiate the effects of online delivery from those of ERP. The reason(s) for selection of only the YGTSS-TTSS score as the primary outcome in the included studies, rather than the YGTSS-Impairment score, is unclear. Currently available data for Neupulse refer to stimulation delivered for a maximum period of four weeks.

Published transition probabilities were not available for Neupulse and the intervention cost that might be incurred if the device were used in NHS practice is unclear. Economic modelling required several major assumptions around the most appropriate long-term extrapolations of clinical benefit in the model and what, if any, intervention costs would be required to maintain observed treatment effectiveness over the longer term.

***Key areas for future research***

- Replication of studies is needed to confirm observed results
- Future studies should be of longer duration and compare the clinical and cost-effectiveness of digitally enabled with face-to-face behavioural therapy. In addition, inclusion of a non-active intervention such as waitlist would allow the natural course of the disease to be monitored over time
- Future studies should consider the impact of interventions on participants' daily lives as the primary outcome
- Appropriate sub-group analyses according to sex and common comorbidities should be planned in future studies.
- Future studies should include economic evaluations and collect longitudinal data to improve long-term modelling of treatment effectiveness. Emphasis should be placed on determining the impact clinical outcomes on quality of life and costs.

## Background and definition of the decision problem

Tic disorders are neurodevelopmental conditions characterised by fast, irregular, and repetitive muscle movements that can manifest in any part of the body. Tics that affect body movements (e.g., blinking, grimacing, head jerking, head banging, finger clicking) are known as motor tics, while involuntary repetitive sounds, such as grunting, sniffing, or throat clearing are known as vocal or phonic tics. Tic disorders manifest more often in boys than girls with a ratio between 3:1 and 4:1.[1-4] There are several types of tic disorders according to their manifestation and frequency. Transient or provisional tic disorders refer to single or multiple motor and/or vocal tics that have been present for less than 12 months since the first tic onset. Persistent or chronic tic disorders refer to single or multiple motor or vocal tics (but not both) that have persisted for more than 12 months since the first tic onset. Tourette syndrome refers to multiple motor tics and one or more vocal tics that have been present at the same time (but not necessarily concurrently) during the course of the disease and have persisted for more than 12 months since the first tic onset. In all cases, onset is before the age of 18 years and the tics are not attributable to the physiological effects of a substance (e.g., cocaine) or other medical conditions (e.g., Huntington's Disease, post-viral encephalitis).[5]

The mean age of onset for tic disorders is approximately 5 years, although it can be lower in up to 40% of patients.[4, 6] Typically, the severity of tic disorders worsens between 10 and 12 years of age and improves naturally during adolescence and early adulthood.[7, 8] In children and young people, tics tend to come and go, while in adults, they show a more persistent pattern.[9] Psychiatric comorbidities are common among people who suffer from chronic tic disorders.[10] People with Tourette syndrome or chronic tic disorders often experience associated psychiatric conditions such as attention deficit hyperactivity disorder (ADHD; 30 to 54% of people) and obsessive-compulsive disorder (OCD; 10% to 50% of people).[11] Other common comorbidities which are highly associated with comorbid OCD and ADHD in people with chronic tic disorders include mood disorders, disruptive behaviour, and anxiety (30% of people).[6, 11] Comorbid mood disorders tend to be observed more frequently in adolescents and adults than children.[12] Independent from ADHD and OCD comorbidities, Tourette syndrome has also been reported to be associated with an increased risk of anxiety.[6]

Most prevalence studies of Tourette Syndrome have focused specifically on children and young people with few or less reliable data on adults. Internationally, the prevalence of Tourette Syndrome in young people in the community has been reported to be between 0.4% and 3.8%.[2] In the UK, Tourette Syndrome is identified in 1 per 100 school children.[13] A

meta-analysis published in 2012 reported a pooled prevalence rate of 0.77% (95% CI 0.39 to 1.51%) in children (13 studies) and of 0.05% (95% CI 0.03 to 0.08%) in adults (2 studies).[14] A more recent meta-analysis suggested that the adulthood prevalence of Tourette Syndrome is around 118 cases per million adults (95% CI 19-751 cases per million adults) but with considerable heterogeneity between prevalence studies.[15]

Tic disorders can vary in severity and impact various aspects of people's lives, contributing to a reduced quality of life. It is not uncommon for people with tic disorders, particularly when the illness is more severe, to experience serious social issues such as extensive stigma, public avoidance and discrimination.[10, 16] Severe long-lasting tic disorders are also associated with a fourfold increased risk of suicide.[17]

The clinical pathway, management, and treatment options are the same for all tic disorders.

**Current management and clinical pathway**

At present, in the UK, there are specific national guidelines for the assessment, management and referral of neurodevelopmental conditions such as AHDH and autism.[18-20] However, a comprehensive clinical guideline for the diagnosis and management of tic disorders in children and young people does not exist. The NICE Guideline 127 on 'Suspected Neurological Conditions: Recognition and Referral' contains some information on tic disorders and indicates that i) children or young people with tic disorders, that significantly interfere with their ability to function in their daily lives, should be referred to specialist mental health services, neurodevelopmental teams or for neurological assessment; ii) adults with tic disorders should be considered for neurological assessment if their symptoms are severe and the disorder continues to cause distress.[21] Current international guidelines and recommendations include the European Clinical Guidelines for Tourette and Other Tic Disorders, the Canadian Guidelines for the Evidence-Based Treatment of Tic Disorders, Practice Guideline Recommendations Summary for Tourette Syndrome and Chronic Tic Disorders from the American Academy of Neurology, and BMJ Best Practice Tic Disorders.[12, 13, 22, 23]

Symptoms of tic disorders may be reported by people themselves or for children or young people identified by their parents/carers or school educators. In the UK, people with tic disorders attend an initial appointment with a general practitioner (GP) working in primary care. When the presence of a tic disorder is recognised to have a significant impact on

people's quality of life, a referral is usually made to appropriate secondary or tertiary care services (depending on the presentation, comorbidities, and local specialist clinics).[17]

For children and young people, referrals may be made to mental health services (including the Children and Young People's Mental Health Services [CYPMHS]) neurodevelopmental teams, paediatric or neurology teams dependent on local services. For adults, referrals are usually made to neurological services.

As tics may improve with time, the NICE Guideline 127 indicates that for individuals presenting in primary care a watch-and-wait approach is considered acceptable, especially for those who do not experience any functional impairment.[21]

Current practice varies between countries and according to the availability of local services but, in general, treatment options for chronic tic disorders include psychoeducation, behavioural therapy, pharmacological therapy, and deep brain stimulation.

**Psychoeducation** for patients, their families, teachers, and peers, which aims to reduce stigma and distress and increase awareness of the illness, is regarded as the initial approach to treating all tic disorders. This includes information on the natural waxing and waning course of the disorder, which is favourable in most cases, on what can worsen tics such as stress, anxiety, and excitement and on the importance of avoiding focusing on the presence of tics. An assessment of concomitant psychiatric and mood disorders (e.g., ADHD, OCD, autism spectrum disorder, anxiety) should also be considered as these may further aggravate the patients' emotional, behavioural, and social functioning.[13] In many cases, people with tic disorders may not require further treatment aside from psychoeducation and observation (watch and wait approach).

However, it has been reported that in the UK psychoeducation is rarely provided by general practitioners in the first appointment and many people with tic disorders do not receive advice on how to manage their tics or information on treatment options.[17]

Current international guidelines recommend the use of **behavioural therapy** as the first-line intervention for tic disorders in both children and young people and adults.[12, 22-24] The behavioural approaches with more robust evidence of efficacy are habit reversal training (HRT), comprehensive behavioural intervention for tics (CBIT) and the efficacy of exposure with response prevention (ERP).[12] With HRT the patient is trained to perform a voluntary movement, which is physically incompatible with the performance of the tic until the urge

(unpleasant internal stimulus) to perform the tic goes away. The CBIT utilises the same components of HRT alongside relaxation training and functional interventions to tackle factors that may provoke or exacerbate tics. The ERP aims to break the association between the urge and the tic by asking the patient to suppress the tics for prolonged periods using various cognitive tools.[23] However, due to a shortage of trained therapists, behavioural therapy is only available in a small number of specialist centres and only about 20% of people with tic disorders have access to it.[17] Therefore, digitally enabled interventions have the potential to improve access as well as equity of access to treatment for people with tic disorders.

Concerning **pharmacological therapy,** there is some evidence that a2-adrenergic receptor agonists (e.g., clonidine, guanfacine) and antipsychotic drugs (e.g., risperidone, haloperidol) are effective in the short term.[25-27] Antipsychotic drugs due to their adverse effect profile are mostly considered for the treatment of severe tics when a2-adrenergic receptor agonists are not effective or not tolerated. The decision about the type and dosage of pharmacological therapy should be provided by a health professional with experience in the management of tic disorders after taking into consideration the presence of comorbidities, which may affect the patient's treatment response.

**Deep brain stimulation (DBS)** in specialised centres has been proposed for patients with severe tics that are refractory to behavioural and pharmacological interventions.[12, 13] There is, however, little information on the effects of DBS in children and young people with chronic tic disorders to support its use in clinical practice.[23] The largest DBS randomised cross-over trial published in 2015 indicated some possible benefits for adults with Tourette Syndrome but also highlighted several methodological challenges in the design of brain stimulation studies.[12, 28, 29] Similarly, the prospective International Deep Brain Stimulation Database and Registry published in 2018, which included 185 patients with medically refractory Tourette syndrome who underwent DBS implantation, showed that DBS was associated with improvement in patients' symptoms but also with important adverse events.[30]

Alternative treatments such as dietary supplements, fish oils, acupuncture and antibiotics have also been proposed for tic disorders, but the rationale and evidence of their efficacy is still unclear or insufficient.

Novel treatment options such as median nerve stimulation (MNS) are currently under investigation. Results from a recent open-label comparative study assessing 27 people (15-64

years of age) with chronic tic disorders suggest that MNS may improve the frequency and intensity of tics with minimal side effects.[31]

**Description of the technologies of interest**

The technologies considered for this appraisal are digital technologies that enable the remote/online delivery of therapeutic intervention to people with chronic tic disorders or Tourette Syndrome. These interventions should only be considered provided the person (and parent or carer where appropriate) have had access to a form of psychoeducation. If the tic disorder continues to cause difficulties, a clinician may consider referring people for these proposed interventions. These technologies should have received or are likely to receive appropriate regulatory approval (e.g., CE mark / UKCA mark and DTAC compliance), should be available or likely to be soon available to the NHS and should have online guided contact with a practitioner as part of the programme, or clinician oversight with the intervention for user safety. We have identified two digitally enabled technologies for the treatment of people with chronic tic disorders: **Online Remote Behavioural Treatment for Tics (ORBIT)** and **Neupulse.**

**ORBIT (MindTech)** is an online therapeutic intervention which aims to reduce tic severity in children and young people with tic disorders. The ORBIT treatment programme was developed from an existing research platform (BIP TIC) in Sweden, which was designed to be age-appropriate in appearance for use by children and their parents and included animations and interactive scripts. The platform has been used to deliver internet-based therapy for conditions such as phobia, anxiety and OCD. ORBIT provides a form of behavioural therapy called exposure and response prevention (ERP), which is supported by an online therapist across a 10-week program. It is delivered on a secure internet platform and includes 10 self-help guided chapters followed by exposure and response prevention tasks. Through the ORBIT programme, patients practise controlling their tics for increasingly long periods and then deliberately provoke urges while not releasing any tics. Related interventions are delivered to the patient's parent/supporter on the same time scale. The therapist has 10 to 20 minutes of contact time with the family each week and promotes engagement with the intervention as well as answering any questions rather than delivering therapeutic content.[32-34] ORBIT has been studied as part of NIHR-funded UK-based trials which have reported it to be a clinically and cost-effective intervention at up to 18 months.[33, 34] ORBIT does not require CE marking as it is not considered a medical device. At present, the investigators are working towards DTAC compliance.

**Neupulse** (developed by Neurotherapeutics Ltd) is a wearable wrist-worn neuromodulation device with a corresponding phone app which provides a novel approach to reduce tic frequency and severity. The device addresses the imbalances in neural activity which are associated with tics and premonitory urges by modulating neural oscillations within the brain's sensorimotor networks. No active effort is required of the user to reduce these symptoms, (besides turning on the device) which delivers low-intensity electrical pulses to the median nerve (median nerve stimulation). Currently, the device has been assessed for children and young adults aged 12 and over with suspected or diagnosed Tourette Syndrome or a chronic (motor or vocal) tic disorder.

Median nerve stimulation (MNS) is a type of Transcutaneous electrical nerve stimulation (TENS) delivered to the wrist. TENS has a long history of therapeutic use and TENS machines are widely available over the counter for use within the community. The Neupulse device produces low-intensity electrical stimulation up to a maximum of 14mA. It has been shown within a UK double-blind-sham control trial to reduce tic frequency when the stimulation is turned on and to be clinically effective with 4 weeks of once-a-day 14-minute use.[35] The rhythmic pattern of medial nerve stimulation used by Neupulse has been shown to increase brain activity associated with movement suppression, without impairing intentional movement or cognitive function.[35, 36] The device currently under development for over-the-counter sale will be supported by written and video-based guidance and a technical support helpline. Neupulse is working towards CE and UKCA marking, and it is estimated that the device will be available in 2026.

**Population and relevant subgroups**

The population of interest is people with a diagnosed primary tic disorder who have had access to psychoeducation; however, their tics continue to be bothersome to them.

Where data permit, the following subgroups were considered:

- Children and young people with diagnosed comorbidities, including attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), autism spectrum disorder (ASD), mood disorders, and anxiety.
- Adults with chronic tic disorders.

**Aim and Objectives**

This assessment aims to establish whether *digitally enabled therapy for people with chronic tic disorders and Tourette Syndrome represents a clinically and cost-effective use of NHS resources.*

The specific objectives are:

- To evaluate the safety and effectiveness of digitally enabled non-pharmacological therapy for treating chronic tic disorders and Tourette Syndrome in UK clinical practice;
- To develop an economic model to assess the cost-effectiveness of digitally enabled technologies for the non-pharmacological treatment of chronic tic disorders that are available or likely to become available in UK clinical practice.

**Table 1 Summary of the characteristics of the devices considered for this assessment**

| Device name | ORBIT (MindTech) | Neupulse (Neurotherapeutics) Clinical trial | Neupulse (Neurotherapeutics) Current medical device |
|---|---|---|---|
| **Platform** | Delivered remotely via the BIP (*Barninternetprokektet*, Swedish for *Child Internet Project*; http://www.bup.se/BIP/) technical platform, a Swedish web-based platform specifically designed for use by children and their parents with an age-appropriate appearance, animations and interactive scripts. The platform can be accessed via the internet using a smartphone, desktop computer or laptop. | Wrist worn stimulation device designed and approved for a home use trial by the MHRA. | Wrist worn wearable device with hydrogel pad to provide median nerve stimulation. An accompanying mobile phone app is used to setup and adjust the device. |
| **Type of behavioural therapy** | Exposure and response prevention (ERP). ERP aims to break the urge-tic-relief cycle of reinforcement whilst promoting tolerance of premonitory urges and tic suppression. The intervention is delivered in 10 chapters split into child intervention and parent/supporter intervention:<br>1. Learn about tics/introduction<br>2. More about tics/thoughts and behaviours of supporters<br>3. Practising stopping your tics/praise | Neuromodulation of the brain's sensorimotor networks using low intensity (1-19mA) 10Hz transcutaneous electrical nerve stimulation (TENS) delivered to the median nerve (Median nerve stimulation). | Transcutaneous electrical stimulation (TENS) to the median nerve stimulation at a frequency of 10Hz with intensity levels (1-14mA) adjustable via a mobile phone App. |

| Device name | ORBIT (MindTech) | Neupulse (Neurotherapeutics) Clinical trial | Neupulse (Neurotherapeutics) Current medical device |
|---|---|---|---|
| | 4. Making the practice more challenging/prompts<br>5. Continued practice/situations and reactions<br>6. School/troubleshooting<br>7. Talk about your tics/continued practice<br>8. Continued practice/continued practice<br>9. The final sprint/continued practice<br>10. Plan for the future/plan for the future | | |
| **Aim of therapy** | ERP aims to break the urge-tic-relief cycle of reinforcement whilst promoting tolerance of premonitory urges and tic suppression. | Immediate reduction in tic frequency and complexity during device use and reduction of tic severity after four weeks of use. | Immediate reduction of urge to tic and tic intensity |
| **Duration** | 10 weeks. | The therapy aims to address the imbalances in neural activity which are associated with tics and premonitory urges by modulating neural oscillations within the brain's sensorimotor networks. The trial device was pre-programmed to deliver once a day rhythmic trains of low intensity electrical stimulation in bursts of 2 minutes of stimulation followed by 1 minute of no stimulation for 14 minutes. Users were | Intermittent on demand (1 hr session) up to 8 hours depending on battery life<br><br>Stimulation can be activated "on demand" by users with a maximum individual session time of 1hr. Session parameters can be adjusted via the app. The default session provides burst stimulation comprising 2 minutes of stimulation followed by 1 minute of no stimulation. |

| Device name | ORBIT (MindTech) | Neupulse (Neurotherapeutics) Clinical trial | Neupulse (Neurotherapeutics) Current medical device |
|---|---|---|---|
| | | instructed to use the device at home for five days a week for a month. | |
| **Contact with therapist** | Remote contact; at least once a week via messages sent inside the treatment platform (resembling an email). The therapist's role is to encourage uptake and adherence to the programme plus troubleshooting and technical support rather than delivering therapeutic content. | Remote video: Weekly contact. The therapist completed weekly clinical assessments. | Over the counter – no prescription required.<br>No contact with the therapist is required.<br>App can collate symptom monitoring data for review by an HCP.<br>Technical support available.<br>Change to the pathway is required – as people with TS find it hard to access HCPs. |

Note. HCP: healthcare professionals

## Assessment of clinical effectiveness

### Systematic review methods

An objective synthesis of the evidence to evaluate the safety and effectiveness of digitally enabled non-pharmacological therapy as compared to standard care for treating chronic tic disorders and Tourette Syndrome in UK clinical practice. This assessment was conducted according to current methodological standards. The methods were pre-specified in a research protocol (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024508045).

#### *Identification of studies*

An Information Specialist developed a comprehensive literature search strategy to identify relevant published peer-reviewed studies. Major electronic databases were searched, including MEDLINE, Embase, Cochrane Library, Web of Science, and CINAHL. The focus of the search initially was on the approved devices listed in the NICE final scope; search facets defining the population of interest were included. There were no restrictions on the date or language of publication at the time of the search. The reference lists of studies selected for full-text appraisal were screened for additional studies. Major clinical trial registries were searched to identify relevant ongoing trials. Websites of manufacturers of appropriate technologies, professional organisations and regulatory bodies were searched to identify additional relevant reports. Any further information on potentially relevant evidence provided by the manufacturers of the technologies of interest was also considered. All references were exported to Endnote for recording and deduplication. A draft MEDLINE search is detailed in Appendix 1. The MEDLINE search was adapted to search other electronic databases.

#### *Inclusion and exclusion criteria*

The eligibility criteria for the review of clinical effectiveness evidence are summarised in Table 2.

**Table 2 Eligibility criteria for the review of clinical effectiveness evidence**

| | |
|---|---|
| **Population of interest** | Children/young people and adults diagnosed with a confirmed primary, chronic tic disorder |
| **Clinical condition** | Primary, chronic tic disorders including Tourette Syndrome.<br><br>Transient and secondary tic disorders and functional tic-like behaviours were not considered eligible for inclusion. |
| **Technologies under investigation** | • ORBIT (MindTech)<br>• Neupulse (Neurotherapeutics) |
| **Comparator intervention** | Standard care, including psychoeducation and face-to-face behavioural therapy. |
| **Outcome measures** | **Intermediate outcome measures**<br>• Intervention-related adverse events<br>• Treatment satisfaction and engagement<br>• Intervention adherence, rates of attrition and completion<br><br>**Clinical outcome measures**<br>• Measures of symptom severity (self, parental or practitioner reported) using validated instruments such as the YGTSS.<br>• Tools for depression and anxiety such as Patient Health Questionnaire for adolescents, Children's Depression Inventory and Beck Depression Inventory<br>• Social, behavioural, and functional outcomes<br>• Suicidal thoughts and behaviour<br><br>**Patient-reported outcome measures**<br>• Health-related quality of life<br>• Patient's experience and patient's satisfaction<br>• Rates and reasons for attrition |
| **Study design** | Clinical studies assessing the efficacy or effectiveness of non-pharmacological treatment delivered remotely or online using digital technologies.<br>We included RCTs, and comparative non-randomised studies published in English. Articles available in their pre-publication version and relevant reports submitted by the manufacturers of the technologies under investigation were considered for inclusion. Crossover studies (phase before crossover) and evidence from uncontrolled studies (in the absence of evidence from comparative studies) were also considered eligible. Conference abstracts were excluded because they were not considered to provide sufficient information. |
| **Healthcare setting** | Secondary care settings (e.g., CYPMHS)<br>Tertiary care settings (e.g., neurology or neurodevelopmental teams - including neurologists, neuropsychologists, psychiatrists, psychologists, specialist nurses, speech and language therapists). |

***Study selection and data extraction***

One reviewer (MC) screened all citations identified by the search strategies. A second reviewer (MB) independently screened a random 20% sample (selected using a random number generator, random.org, with selection based on numerical position in the list of citations). Two reviewers (MC, MB) independently assessed each full-text article for eligibility. Reasons for exclusion were documented. The research protocol specified that data extraction had to be conducted by two independent reviewers. However, due to time and resource constraints, one reviewer (MC) extracted data, which was subsequently cross-checked by a second reviewer (MB). A customised Excel data extraction spreadsheet was developed for this assessment. The following information was recorded from each study:

1. Characteristics of studies: first author, year of publication, country, language, setting, inclusion and exclusion criteria.
2. Characteristics of study participants: age, sex, tic typology, comorbidities, number of enrolled participants, number of participants analysed, number of dropouts and reasons for withdrawal, setting.
3. Characteristics of the intervention: digital platform, details of the technology, content of therapy, structure and number of sessions to be completed, duration, type and frequency of contact with a therapist, and therapist's level of expertise.
4. Characteristics of the comparator/control intervention: nature and mode of delivery, duration, type and frequency of contact with a therapist, and therapist's level of expertise.
5. Relevant patient-reported, clinical and intermediate outcome measures, and information related to the use of digital technologies.

At all stages, disagreements were resolved through discussion.

***Data synthesis***

The findings of each included study were tabulated and summarised narratively for each outcome of interest. We combined results from two of the included studies that were considered sufficiently similar in terms of intervention/comparator, participants and outcome measures.[33, 37] We conducted random-effects model meta-analyses to pool unadjusted mean difference and 95% CIs for the total tic severity score (TTSS) and the impairment score of the YGTSS using the inverse variance method. It is worth noting that the TTSS score of the YGTSS ranges from 0 to 50 and measures the severity of the tic disorders (where 50 indicates higher severity). The YGTSS impairment score (YGTSS-Impairment) also ranges from 0 to

50. A score of 0 indicates that the presence of Tourette syndrome has no negative impact on a person's daily life. In contrast, a score of 50 indicates considerable interference and disability associated with the presence of Tourette syndrome. Heterogeneity between studies was assessed using the $I^2$ statistic. Statistical analyses were conducted using the Cochrane software for systematic reviews and meta-analysis (RevMan Web). When appropriate, the following subgroups were considered: children with diagnosed co-morbidities (ADHD, OCD, autism spectrum disorder, mood disorders, anxiety) and adults with chronic tic disorders.

**Assessment of risk of bias**

The Cochrane Risk of Bias tool (version 2) was used to assess the risk of bias for the primary outcome measured by the YGTSS-TTSS in the RCTs included in the review.[38] One reviewer (MC) assessed each included study, and a second reviewer (MB) cross-checked the assessments. Disagreements were resolved by consensus.

**Results of the assessment of clinical effectiveness**

***Results of the literature searches***

The literature searches identified 379 titles/abstracts. Three further studies were identified: one (Maiquez 2020)[39] was identified from a reference list (Maiquez 2023)[35], one was provided by the corresponding author of the Maiquez 2023 study (Andren 2024)[40] and the third[41] was identified from the website search. A total of 40 publications were selected for full-text screening of which 14 met our inclusion criteria, reporting a total of three studies. The Andren 2024 study was out with our search dates but was included as a secondary publication to Andren 2022[37] for completeness. A PRISMA flow diagram detailing the process of study selection is presented in Figure 1.

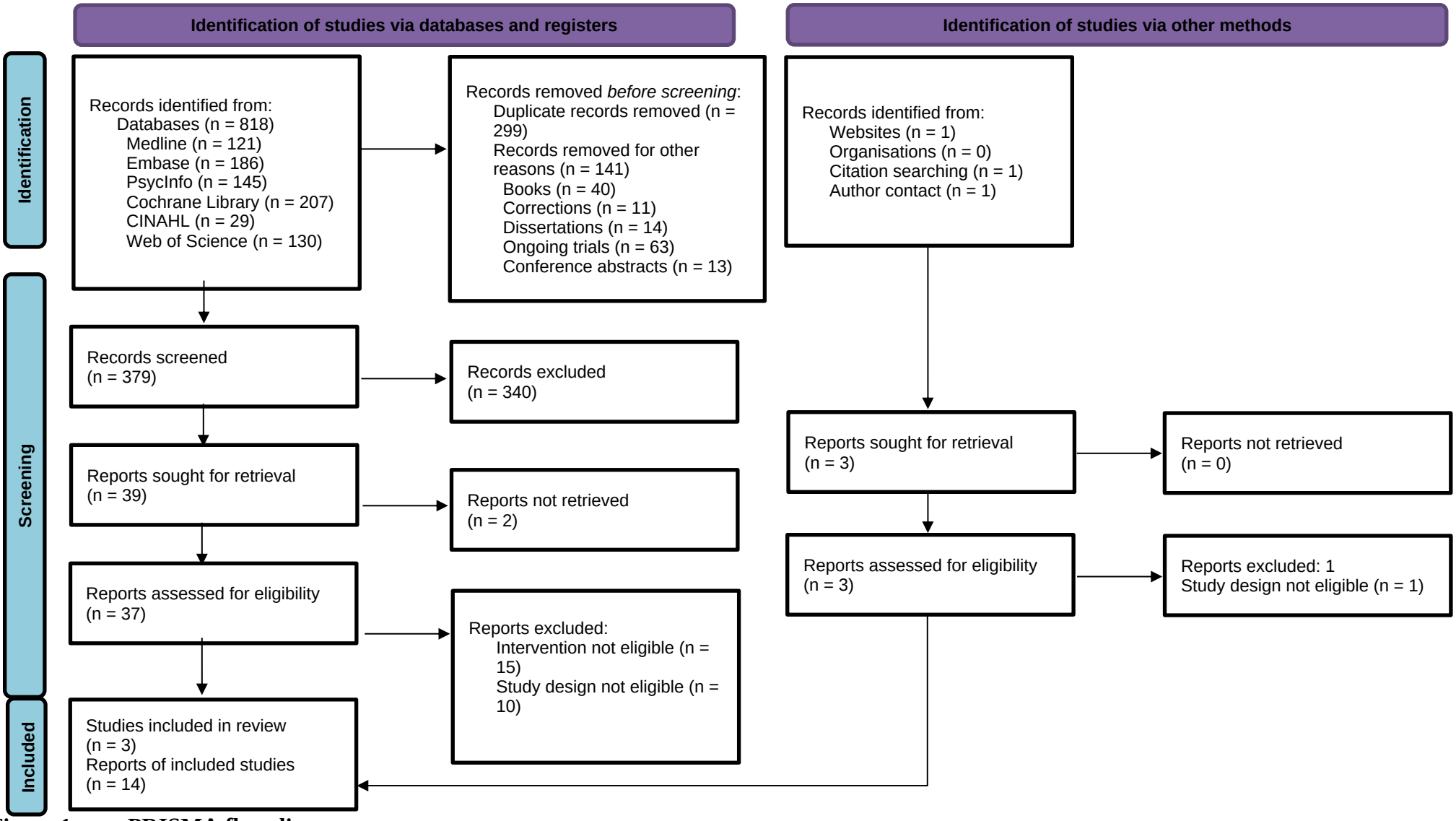


**Figure 1 PRISMA flow diagram**

### *Characteristics of included studies*

A total of three RCTs reported in 14 publications were included in the review of clinical effectiveness evidence. Characteristics of the included studies are presented in Appendix 2. Two studies compared ORBIT with psychoeducation; one was conducted in the UK[33] and the other in Sweden.[37] The third study was UK-based and compared Neupulse active stimulation with sham stimulation; this trial also included an open-label waitlist (treatment as usual) control condition which is reported here for completeness.[35] All three were published in English language and full-text form. The two ORBIT studies recruited children and young people aged 9 to 17 years.[33, 37] The Neupulse study recruited people aged 12 years upwards.[35] A total of 566 participants were randomised (UK ORBIT: 224[33], Swedish ORBIT: 221[37]; Neupulse: 121[35]). Longest follow-up periods in the ORBIT studies were 18 months (UK ORBIT[33]) and 12 months (Swedish ORBIT[37]).

*Evidence gap: Evidence was not available to compare the interventions under investigation and face-to-face behavioural therapy, the current standard of care. The comparator in the two ORBIT studies was psychoeducation, while the Neupulse active stimulation arm was compared to sham stimulation and a waitlist group. Both ORBIT trials did not include a non-active control group (e.g., waitlist).*

### *Characteristics of participants*

Baseline characteristics of participants in the included studies are reported in Table 4. The mean age of participants was between 12.0 years and 12.4 years in the two ORBIT studies[33, 37] and between 23.5 years and 24.4 years in the Neupulse study.[35] The proportion of male participants ranged from 64.0% to 80.4% in the ORBIT studies and 59.0% to 63.4% in the Neupulse study. Regarding tic typology, most participants in the UK ORBIT study had both motor and vocal tics (92% and 95% in the intervention and comparator groups, respectively), while 8% and 5%, respectively had motor tics only and none had only vocal tics.[33] In the Swedish ORBIT study, most participants had Tourette Syndrome (93.7% and 89.1% in the intervention and comparator groups, respectively).[37] A further 6.3% and 8.2%, respectively, had chronic motor tic disorder and 2.7% of participants in the comparator group had chronic vocal tic disorder. Tic typology in the Neupulse study was not reported. Comorbidities reported by the studies included ADHD (ranging from 12.7%[37] to 24.4%[35]), anxiety disorder (ranging from 13.6%[37] to 30.8%[35]) and OCD (ranging from 3%[33] to 41.5%[35]).

*Evidence gap: The Neupulse study was the only study included in the review to recruit adults. The maximum age of participants in the two ORBIT trials was 17 years and the materials were developed accordingly. However, with adaptation, ORBIT may be suitable for adults.*

*Uncertainty: The proportion of participants with Tourette Syndrome in the UK ORBIT trial was not reported. The mean baseline tic severity measured using the YGTSS-TTSS scores was slightly higher in the UK ORBIT study than in the Swedish study; however, both trials described the participants' severity of tic disorders as moderate to severe.*

*Uncertainty: It was unclear whether the participants in the two ORBIT trials had access to psychoeducation prior to recruitment into the trials. Access to psychoeducation was not an inclusion criterion for either trial.*

**Table 3 Baseline characteristics of participants in included studies**

| Study ID | Intervention group (n analysed) | Age, years, mean (SD) | Male sex, % | White ethnicity, % | Tic typology, n (%) | Comorbidities, n (%) |
|---|---|---|---|---|---|---|
| **Hollis 2021[33] (ORBIT UK)** | ERP (n=112) | 12.2 (2.0) [age of tic onset: NR] | 80.4 | 86 | Both motor and vocal tics: 103 (92)<br>Motor tics only: 9 (8)<br>Vocal tics only: 0 (0) | Anxiety disorder: 34 (30)<br>ADHD: 26 (23)<br>Oppositional defiant disorder: 26 (24) [n=110]<br>Autism spectrum disorder: 9 (8) [n=111]<br>OCD: 8 (7)<br>Major depression: 2 (2)<br>Conduct disorder: 3 (3) [n=110] |
| | Psychoeducation (n=112) | 12.4 (2.1) [age of tic onset: NR] | 77.7 | 88 | Both motor and vocal tics: 106 (95)<br>Motor tics only: 6 (5)<br>Vocal tics only: 0 (0) | Anxiety disorder: 27 (24)<br>ADHD: 25 (22)<br>Oppositional defiant disorder: 23 (21) [n=111]<br>Autism spectrum disorder: 4 (4)<br>OCD: 2 (3)<br>Major depression: 6 (5)<br>Conduct disorder: 2 (2) [n=111] |
| **Andren 2022[37] (ORBIT Sweden)** | ERP (n=111) | 12.0 (2.3) [age of tic onset: 5.7] | 64.0 | NR | Tourette syndrome: 104 (93.7)<br>Chronic tic disorder motor: 7 (6.3)<br>Chronic tic disorder vocal: 0 | Any: 44 (39.6)<br>ADHD: 20 (18.0)<br>Anxiety disorder: 16 (14.4)<br>OCD: 11 (9.9)<br>Depression: 1 (0.9)<br>Other: 7 (6.3) |
| | Education (n=110) | 12.1 (2.3) [age of tic onset: 6.2] | 73.6 | NR | Tourette syndrome: 98 (89.1)<br>Chronic tic disorder motor: 9 (8.2)<br>Chronic tic disorder vocal: 3 (2.7) | Any: 40 (36.0)<br>ADHD: 14 (12.7)<br>Anxiety disorder: 15 (13.6)<br>OCD: 6 (5.5)<br>Depression: 3 (2.7)<br>Other: 3 (2.7) |

| Study ID | Intervention group (n analysed) | Age, years, mean (SD) | Male sex, % | White ethnicity, % | Tic typology, n (%) | Comorbidities, n (%) |
|---|---|---|---|---|---|---|
| **Maiquez 2023[35] (Neupulse)** | Active stimulation (n=41) | 23.5 (12.6) [age of tic onset: 7.0] | 63.4 | NR | NR | ADHD: 10 (24.4)<br>OCD: 17 (41.5)<br>Autism spectrum disorder: 8 (19.5)<br>Anxiety disorder: 9 (22.0) |
| | Sham stimulation (n=39) | 24.0 (13.4) [age of tic onset: 8.4] | 59.0 | NR | NR | ADHD: 9 (23.1)<br>OCD: 8 (20.5)<br>Autism spectrum disorder: 9 (23.1)<br>Anxiety disorder: 12 (30.8) |
| | Waitlist (n=41) | 24.4 (12.6) [age of tic onset: 7.5] | 63.4 | NR | NR | ADHD: 8 (19.5)<br>OCD: 12 (29.3)<br>Autism spectrum disorder: 2 (4.9)<br>Anxiety disorder: 11 (26.8) |

Note. ERP: exposure and response prevention; ADHD: attention deficit hyperactivity disorder; OCD: obsessive compulsive disorder, NR: not reported. The waitlist group on the Neupulse study is not included in the clinical effectiveness review but is reported for completeness

### *Risk of bias assessments*

Figure 2 presents a summary of the risk of bias assessments of the three included studies for the YGTSS-TTSS primary outcome.

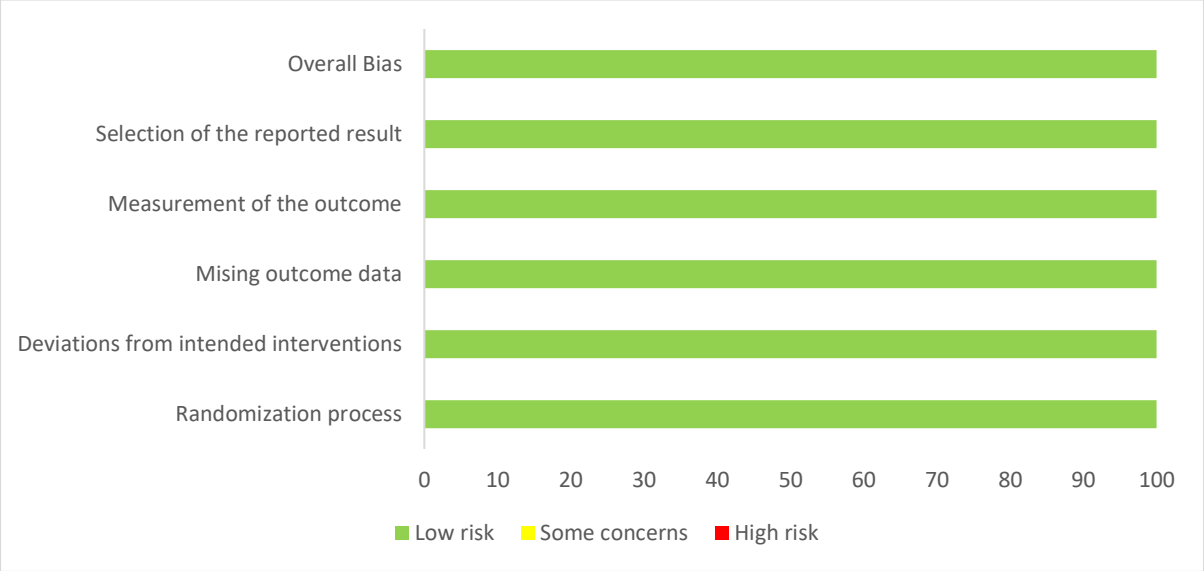


**Figure 2 Summary of risk of bias assessments for the three included studies**

Risk of bias assessments of individual studies is presented in Figure 3.

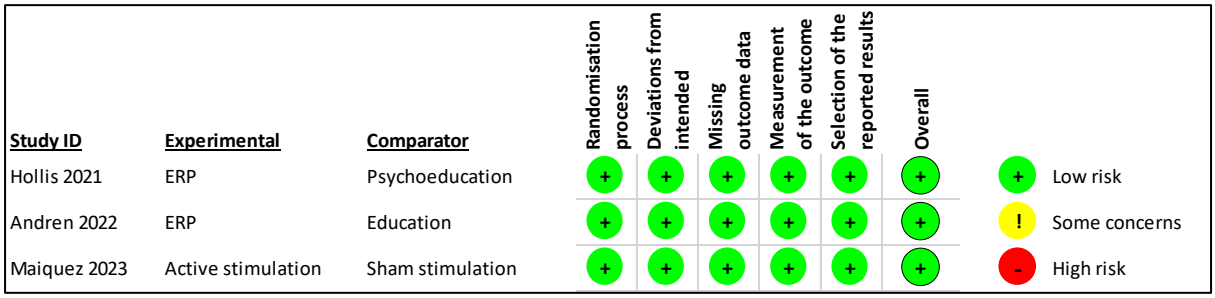


**Figure 3 Risk of bias assessments of individual studies**

According to the Cochrane risk of bias tool (version 2), the overall risk of bias was low for the three trials.[33, 35, 37] All three were appropriately randomised, there was no evidence of deviations from the intended interventions, missing outcome data was low, accounted for and balanced across groups, the outcome and its assessment were appropriate and there was no evidence of selected reporting.

### *Clinical effectiveness results*

**Clinical outcomes**

The primary outcome of all three studies was total tic severity assessed by the tic severity score (TTSS) of the Yale Global Tic Severity Scale (YGTSS) scale in the two ORBIT studies[33, 37] and by the tic severity score (TTSS) of the Yale Global Tic Severity Scale revised (YGTSS-R) in the Neupulse study.[35] Tables 4 and 5 present the YGTSS-TTSS outcome data from the two ORBIT studies and the Neupulse study, respectively. The improvements in tic severity in the intervention group in the Hollis 2021 study were described by the authors as clinically important, considering an average of 0.5 of a standard deviation between the intervention and comparator as being clinically important.[33] The authors of the Neupulse study defined a clinically meaningful reduction in tic severity as reduction of 25 percentiles or greater in YGTSS-TTSS scores, and reported a substantially greater proportion of the active stimulation group (59.0%) as responders than the sham stimulation group (33.3%; OR 2.9, 95%CI 1.1, 7.2).

Tables 6 and 7 report further clinical outcomes from the two ORBIT studies and the Neupulse study, respectively.

**Table 4 YGTSS-TTSS data reported in the two ORBIT studies**

| Study ID | Time point | ORBIT | Psychoeducation | Difference between groups at time point |
|---|---|---|---|---|
| **ORBIT** | | | | |
| Hollis 2021[33] | Baseline | 28.4 (7.7) | 28.4 (7.1) | N/A |
| | 3 months | 23.9 (8.2) | 26.8 (7.3) | Estimated difference: -2.29 (95% CI -3.86, -0.71)<br>Effect size -0.31 (-0.52, -0.10) |
| | 6 months | 21.5 (8.8) | 25.0 (7.6) | Estimated difference: -2.64 (95% CI -4.56, -0.73)<br>Effect size -0.36 (-0.62, -0.10) |
| | 12 months | 21.7 (8.8) | 24.9 (7.3) | Estimated difference -2.64 (95% CI -4.48, -0.79)<br>Effect size -0.36 (95% CI-0.61, -0.11) |
| | 18 months | 21.5 (9.0) | 23.9 (8.4) | Estimated difference -2.01 (95%CI -3.86, -0.15)<br>Effect size -0.27 (95% CI -0.52, -0.02) |
| Andren 2022[37] | Baseline | 22.25 (5.60) | 23.01 (5.92) | N/A |
| | 3 months | 16.17 (6.82) | 17.72 (7.11) | ITT linear quantile mixed model coefficient -0.53 (95%CI -1.28, 0.22)<br>Effect size 0.11 (95% CI -0.09, 0.30), p=0.17 |
| | 6 months | 16.06 (6.98) | 17.23 (8.18) | NR |
| | 12 months | 14.93 (7.70) | 16.73 (8.30) | Interaction between treatment and time coefficient -0.38 (95% CI -1.11, 0.35), p=0.30<br>Effect size 0.13 (95% CI -0.12, 0.37) |

Note. YGTSS-TTSS, Yale Global Tic Severity Scale – Total Tic Severity Score. Data reported as mean (SD)

**Table 5 YGTSS-TTSS data reported in the Neupulse study**

| Study ID | Time point | Active stimulation | Sham stimulation | Waitlist | Difference between groups at time point |
|---|---|---|---|---|---|
| **NEUPULSE** | | | | | |
| Maiquez 2023[35] | Baseline | 40.1 (7.0) | 39.5 (6.3) | 38.9 (6.9) | N/A |
| | 4 weeks | Mean (SD) reduction 7.13 (1.1) | Mean (SD) reduction 2.13 (0.32) | Mean (SD) reduction 2.26 (0.34) | Active vs sham: Observed difference -5, effect size -0.47 (95%CI -0.94, -0.02), p=0.02<br><br>Active vs waitlist: Observed difference -5, effect size -0.48 (95%CI -0.97, -0.04), p=0.02 |

Note. YGTSS-TTSS, Yale Global Tic Severity Scale – Total Tic Severity Score. The waitlist group is not included in the clinical effectiveness review but is reported for completeness. Data reported as mean (SD) unless otherwise specified

**Table 6 Clinical outcomes from the two ORBIT studies**

| Study ID | Time point | ORBIT | Psychoeducation | Difference between groups at time point |
|---|---|---|---|---|
| **YGTSS-Impairment, mean (SD)** | | | | |
| Hollis 2021[33] | Baseline | 23.8 (10.3) | 22.9 (9.9) | N/A |
| | 3 months | 16.7 (10.4) | 19.1 (10.9) | Estimated difference (95% CI) -2.24 (-4.82, 0.33)<br>Effect size -0.22 (-0.48, 0.03) |
| | 6 months | 14.7 (10.7) | 17.0 (10.5) | Estimated difference (95% CI) -1.95 (-4.68, 0.78)<br>Effect size -0.19 (-0.46, 0.08) |
| | 12 months | 14.8 (11.6) | 17.5 (11.1) | Estimated difference (95% CI) -2.41 (-5.35, 0.53)<br>Effect size -0.24 (-0.53, 0.05) |
| | 18 months | 15.8 (11.5) | 16.9 (12.1) | Estimated difference (95% CI) -0.97 (-3.93, 1.99)<br>Effect size -0.10 (-0.39, 0.20) |

| Study ID | Time point | ORBIT | Psychoeducation | Difference between groups at time point |
|---|---|---|---|---|
| Andren 2022[37] | Baseline | 18.38 (7.08) | 18.73 (7.79) | N/A |
| | 3 months | 7.68 (8.82) | 8.70 (8.10) | ITT linear quantile mixed model coefficient -0.26 (-1.70, 1.18), p=0.72<br>Effect size (95% CI) 0.05 (-0.34, 0.44) |
| | 6 months | 6.85 (7.81) | 7.84 (8.97) | NR |
| | 12 months | 6.54 (8.14) | 6.14 (8.12) | Interaction between treatment and time coefficient 0.16 (95% CI -0.55, 0.86), p=0.67<br>Effect size 0.03 (95% CI -0.14, 0.20) |
| **Parent tic questionnaire (PTQ)** | | | | |
| Hollis 2021[33] | Baseline | 54.7 (29.9) | 53.1 (26.1) | N/A |
| | 3 months | 34.7 (26.4) | 45.7 (25.5) | Estimated difference (95% CI) -9.44 (-15.37, -3.51)<br>Effect size -0.34 (-0.55, -0.13)** |
| | 6 months | 31.1 (21.6) | 40.6 (24.3) | Estimated difference (95% CI) -8.60 (-14.43, -2.77)<br>Effect size -0.31 (-0.51, -0.10)** |
| | 12 months | 30.7 (23.8) | 43.0 (25.3) | Estimated difference (95% CI) -9.89 (-16.01, -3.77)<br>Effect size -0.35 (-0.57, -0.13)** |
| | 18 months | 28.1 (19.1) | 35.9 (25.6) | Estimated difference (95% CI) -2.15 (-8.83, 4.53)<br>Effect size -0.08 (-0.31, 0.16) |
| Andren 2022[37] | Baseline | 34.33 (19.06) | 38.04 (23.27) | N/A |
| | 3 months | 19.84 (17.92) | 23.51 (18.14) | ITT linear quantile mixed model coefficient 0.13 (95% CI -1.43, 1.68)<br>Effect size (95% CI) -0.01 (-0.22, 0.19) p=0.87 |
| | 6 months | 18.17 (16.18) | 24.18 (20.08) | NR |
| | 12 months | 16.76 (15.97) | 20.76 (17.04) | Interaction between treatment and time coefficient -0.10 (95% CI -1.63, 1.44), p=0.90, effect size 0.02 (95% CI -0.22, 0.26) |
| **Clinical Global Impressions – Improvement Scale (CGI-I)** | | | | |

| Study ID | Time point | ORBIT | Psychoeducation | Difference between groups at time point |
|---|---|---|---|---|
| | | | | |
| Hollis 2021[33] | Baseline | NR | NR | N/A |
| | 3 months | 2.96 (1.1) | 3.37 (1.1) | Estimated difference (95% CI)-0.41 (-0.71, -0.11)<br>Effect size -0.37 (-0.64, -0.10)** |
| | 6 months | 2.8 (1.3) | 3.1 (1.1) | Estimated difference (95% CI) -0.31 (-0.66, 0.03)<br>Effect size -0.29 (-0.61, 0.03) |
| | 12 months | 2.67 (1.09) | 3.07 (0.9) | Estimated difference (95% CI) -0.43 (-0.75, -0.10)<br>Effect size -0.43 (-0.74, -0.12)** |
| | 18 months | 2.49 (1.36) | 2.86 (1.1) | Estimated difference (95% CI) -0.38 (-0.71, -0.05)<br>Effect size -0.35 (-0.66, -0.04)** |
| **Clinical Global Impression Severity scale (CGI-S)** | | | | |
| Andren 2022[37] | Baseline | 4.08 (0.74) | 4.19 (0.72) | N/A |
| | 3 months | 3.24 (0.92) | 3.49 (0.90) | ITT linear quantile mixed model coefficient -0.36<br>(95% CI -0.67, -0.04), p=0.03<br>Effect size (95% CI) 0.71 (0.05, 1.37)** |
| | 6 months | 3.10 (0.93) | 3.32 (1.11) | NR |
| | 12 months | 2.97 (0.96) | 3.25 (1.13) | Interaction between treatment and time coefficient 0.03<br>(95% CI -0.16, 0.21), p=0.28<br>Effect size -0.11 (95% CI-0.80, 0.58) |
| **Children's Global Assessment Scale (CGAS)** | | | | |
| Hollis 2021[33] | Baseline | 70.7 (13.7) | 72.1 (11.8) | N/A |
| | 3 months | 75.9 (12.6) | 75.2 (12.6) | Estimated difference (95% CI) 0.96 (-1.48, 3.41)<br>Effect size 0.08 (-0.12, 0.27) |
| | 6 months | 77.5 (14.7) | 76.8 (12.3) | Estimated difference (95% CI) 0.60 (-2.24, 3.44)<br>Effect size 0.05 (-0.17, 0.27) |
| | 12 months | 77.4 (13.3) | 75.0 (12.9) | Estimated difference (95% CI) 2.85 (0.15, 5.56)<br>Effect size -0.22 (-0.43, -0.01)** |

| Study ID | Time point | ORBIT | Psychoeducation | Difference between groups at time point |
|---|---|---|---|---|
| | 18 months | 79.3 (13.5) | 77.3 (12.6) | Estimated difference (95% CI) 3.18 (0.47, 5.90)<br>Effect size -0.25 (-0.46, -0.04)** |
| Andren 2022[37] | Baseline | 60.60 (6.59) | 60.71 (6.46) | N/A |
| | 3 months | 66.83 (8.64) | 65.72 (7.44) | Intention to treat linear quantile mixed model coefficient 0.67 (95% CI -0.15, 1.49), p=0.11, effect size 0.12 (-0.05, 0.29) |
| **Strengths and difficulties questionnaire** | | | | |
| Hollis 2021[33] | Baseline | 18.0 (6.5) | 16.3 (6.2) | N/A |
| | 3 months | 14.7 (6.1) | 14.2 (6.3) | Estimated difference (95% CI) -0.38 (-1.62, 0.85)<br>Effect size -0.06 (-0.25, 0.13) |
| | 6 months | 15.3 (6.2) | 13.3 (6.1) | Estimated difference (95% CI) 0.57 (-0.93, 2.07)<br>Effect size 0.09 (-0.15, 0.32) |
| | 12 months | 14.4 (5.6) | 14.6 (6.4) | Estimated difference (95% CI) -0.86 (-2.31, 0.58)<br>Effect size -0.13 (-0.36, 0.09) |
| | 18 months | 13.6 (6.1) | 13.8 (5.4) | Estimated difference (95% CI) -0.71 (-2.26, 0.84)<br>Effect size -0.11 (-0.35, 0.13) |
| **Mood and feelings questionnaire** | | | | |
| Hollis 2021[33] | Baseline | 15.9 (1.5) | 16.3 (11.3) | N/A |
| | 3 months | 12.6 (11.1) | 10.7 (11.1) | Estimated difference (95%CI) -1.36 (-3.75, 1.02)<br>Effect size -0.12 (-0.33, 0.09) |
| | 6 months | 11.4 (11.2) | 11.4 (12.1) | Estimated difference (95%CI) -0.61 (-3.85, 2.64)<br>Effect size -0.05 (-0.34, 0.23) |
| | 12 months | 14.3 (11.6) | 11.4 (10.4) | Estimated difference (95%CI) -2.93 (-5.77, -0.09)<br>Effect size -0.26 (-0.51, -0.01)** |
| | 18 months | 16.0 (14.6) | 10.9 (10.0) | Estimated difference (95%CI) -4.87 (-8.00, -1.75)<br>Effect size -0.43 (-0.70, -0.15)** |
| | | | | |

| Study ID | Time point | ORBIT | Psychoeducation | Difference between groups at time point |
|---|---|---|---|---|
| **Spence child anxiety scale** | | | | |
| Hollis 2021[33] | Baseline | 30.5 (17.9) | 32.9 (20.0) | N/A |
| | 3 months | 28.2 (18.3) | 27.2 (19.0) | Estimated difference (95%CI) -2.80 (-6.52, 0.93)<br>Effect size -0.15 (-0.34, 0.05) |
| | 6 months | 25.9 (18.7) | 25.7 (19.6) | Estimated difference (95%CI) -5.10 (-9.70, -0.50)<br>Effect size -0.27 (-0.51, -0.03)** |
| | 12 months | 29.9 (19.1) | 25.3 (17.1) | Estimated difference (95%CI) -6.11 (-10.41, -1.81)<br>Effect size -0.31 (-0.53, -0.08)** |
| | 18 months | 32.6 (20.4) | 24.3 (18.6) | Estimated difference (95%CI) -9.41 (-14.11, -4.70)<br>Effect size -0.49 (-0.74, -0.25)** |

Note. YGTSS, Yale Global Tic Severity Scale. For the study by Hollis 2021, linear regression models were fitted with the study group as the main explanatory variable. The statistical model for CGI-I did not adjust for baseline as it is a model of change. For the Andren 2022 study, outcomes were analysed with linear quantile mixed models, complementary linear mixed models, quantile regression, logistic regression and $chi^2$ tests. The magnitude of the effects is presented as between-group differences in median relative to the interquartile range (for median differences) and as standardized between-group effect sizes (for mean differences, Cohen *d*); **p<0.05. data reported as mean (SD)

**Table 7 Clinical outcomes from the Neupulse study**

| Study ID | Time point | Active stimulation, mean (SD) | Sham stimulation, mean (SD) | Waitlist, mean (SD) | Difference between groups at time point |
|---|---|---|---|---|---|
| **YGTSS-Impairment** | | | | | |
| Maiquez 2023[35] | Baseline | 25.5 (13.7) | 29.8 (13.5) | 30.1 (12.9) | N/A |
| | 4 weeks | NR | NR | NR | Active vs sham: Observed difference 1.07, effect size 0.06 (95% CI -0.39, 0.52), p=0.6<br><br>Active vs waitlist: Observed difference 1.86, effect size 0.11 (95% CI -0.35, 0.58), p=0.7 |
| **YGTSS-motor** | | | | | |
| Maiquez 2023[35] | Baseline | 21.1 (3.2) | 20.4 (3.5) | 20.8 (3.1) | N/A |
| | 4 weeks | NR | NR | NR | Active vs sham: Observed difference -2.03, effect size -0.4 (95% CI -0.85, 0.04), p=0.04**<br><br>Active vs waitlist: Observed difference -2.15, effect size -0.45 (95% CI -0.88, -0.01), p=0.03** |
| **YGTSS-phonic** | | | | | |
| Maiquez 2023[35] | Baseline | 19.0 (4.7) | 19.1 (4.7) | 18.1 (4.7) | N/A |
| | 4 weeks | NR | NR | NR | Active vs sham: Observed difference -3, effect size -0.42 (95% CI -0.87, 0), p=0.04**<br><br>Active vs waitlist: Observed difference -2.72, effect size -0.42 (95% CI -0.85, 0.02), p=0.04** |

| Study ID | Time point | Active stimulation, mean (SD) | Sham stimulation, mean (SD) | Waitlist, mean (SD) | Difference between groups at time point |
|---|---|---|---|---|---|
| **Premonitory Urge for Tics Scale - Revised (PUTS-R)** | | | | | |
| Maiquez 2023[35] | Baseline | 17.9 (8.8) | 19.3 (8.5) | 17.6 (8.6) | N/A |
| | 4 weeks | NR | NR | | Active vs sham: Observed difference at 4w active vs sham: -0.59, effect size -0.05 (95% CI -0.5, 0.39), p=0.4<br><br>Active vs waitlist: Observed difference -2.98, effect size -0.24 (95% CI -0.72, 0.19), p=0.14 |

Note. YGTSS, Yale Global Tic Severity Scale; p<0.05. Data reported as mean (SD)

**Patient reported outcomes**

Health-related quality of life outcomes in terms of C&A-GTS-QOL scores reported by the two ORBIT trials are presented in Table 8 and those from the Neupulse study are presented in Table 9.

**Table 8 C&A-GTS-QOL scores from the two ORBIT studies**

| Study ID | Time point | ORBIT, mean (SD) | Psycho-education, mean (SD) | Difference between groups at time point |
|---|---|---|---|---|
| Hollis 2021[33] | Baseline | 36.6 (16.4) | 35.0 (17.2) | NA |
| | 3 months | 25.7 (18.0) | 31.8 (17.7) | Estimated difference (95% CI) -4.81 (-8.79, -0.83) Effect size -0.29 (-0.52, -0.05)** |
| | 6 months | 27.4 (16.5) | 28.9 (18.3) | Estimated difference (95% CI) -2.91 (-7.60, 1.78) Effect size -0.17 (-0.45, 0.11) |
| | 12 months | 25.5 (16.8) | 32.2 (16.8) | Estimated difference (95% CI) -5.79 (-10.28, -1.30) Effect size -0.34 (-0.61, -0.08)** |
| | 18 months | 26.0 (16.6) | 36.8 (21.1) | Estimated difference (95% CI) -9.00 (-13.98, -4.01) Effect size -0.53 (-0.83, -0.24)** |
| Andren 2022[37] | Baseline | 29.1 (15.1) | 30.5 (16.5) | NA |
| | 3 months | 19.8 (16.3) | 20.1 (15.7) | Coefficient 0.46 (95% CI -1.63, 2.55), Effect size -0.04 (-0.24, 0.16), p=0.67 |
| | 6 months | 18.3 (15.2) | 21.2 (16.7) | NR |
| | 12 months | 20.7 (17.5) | 20.0 (15.2) | Coefficient 0.18 (95% CI -0.98, 1.33), Effect size -0.04 (-0.31, 0.23), p=0.77 |

Note. C&A-GTS-QOL, child and adolescent Gilles de la Tourette quality of life scale; **p<0.05

**Table 9 C&A-GTS-QOL scores from the Neupulse study**

| Study ID | Time point | Neupulse, mean (SD) | Sham stimulation, Mean (SD) | Waitlist, mean (SD) |
|---|---|---|---|---|
| Maiquez 2023[35] | Baseline | 54.9 (24.6) | 52.8 (22.4) | 56.7 (24.1) |
| | 3 months | 46.7 (25.2) | 40.3 (23.6) | 52.1 (24.0) |
| Difference within group at time point | | t=2.64, p<0.015 (baseline vs 3 months) | t=3.9, p<0.0005 (baseline vs 3 months) | t=1.6, p=0.13 (baseline vs 4 weeks) |

Note. C&A-GTS-QOL, child and adolescent Gilles de la Tourette quality of life scale; All QoL data for the Maiquez 2023 study were obtained through personal correspondence with Stephen Jackson

**Intermediate outcomes**

*Adverse events*

The two ORBIT studies reported adverse events. Adverse events were not reported in the Neupulse study. In the UK study, 78.6% of the intervention group and 84.8% of the comparator group experienced an adverse event (AE).[33] It was unclear if they were related to the relevant intervention. In addition, two participants of the comparator group experienced a serious adverse event (one collapse and one tic attack), both of which were deemed unrelated to trial participation. In the Swedish study, 44 treatment-related AEs were reported: depressed mood (n=11), irritability (n=8), anxiety/worry/stress (n=8), conflicts with family/peers (n=5), increased tics (n=4), pain (n=3), tiredness/fatigue/drowsiness (n=2), increased isolation (n=1), restless (n=1), other (n=1).[37] Twenty-one AEs were reported in the comparator group: depressed mood (n=7), anxiety/worry/stress (n=4), increased tics (n=2), irritability (n=2), other (n=2), bullying (n=1), conflicts with family/peers (n=1), physical harm/injury (n=1), hopelessness (n=1). One serious AE unrelated to treatment was reported in the comparator group (meningitis requiring hospitalisation).

*Evidence gap: There was limited reporting of safety evidence in the ORBIT trials, in particular, long-term adverse events. Adverse events were not reported in the Neupulse study.*

*Treatment satisfaction/engagement*

The two ORBIT studies reported indicators of treatment satisfaction or engagement. In the intervention arm of one study, the median number of logins by the young person was 19 as compared to 9 in the comparator group.[33] The median score for the young person's perception of treatment suitability and credibility was 7 in the intervention group and 6 in the comparator group. Mean child satisfaction scores with the ORBIT intervention were 24.8 out of 32, with higher scores indicating higher levels of satisfaction. In the other study, both

children and parents were more satisfied with the ORBIT intervention than the comparator treatment (children: coefficient 3, 95% CI 1.13, 4.87, p=0.003; parents: coefficient 4, 95% CI 2.33, 5.66, p<0.001).[37] The treatment credibility score was identical for children and parents (coefficient 1, 95% CI 0.38, 1.62, p=0.002).

*Intervention adherence*

In the study by Andren 2022, treatment adherence, as measured by the Internet Intervention Patient Adherence Scale (iiPAS), showed no differences between the groups (mid + post-treatment summarised to one score: quantile regression 1 [95%CI -1.28, 3.28, p=0.39)].[37] The Neupulse study did not report adherence data.[35]

*Rates and reasons for attrition*

In the intervention arm of the UK ORBIT study, 23/112 (20.5%) of participants were lost to follow-up at 18 months (13 withdrew, 10 were uncontactable).[33] In the comparator group, 22/112 (19.6%) were lost to follow-up at 18 months (10 withdrew, 12 were uncontactable). In the Swedish ORBIT study, at the 3-month follow-up, three in the intervention arm and two in the comparator arm were lost to follow-up; no reasons were reported.[37] In the Neupulse study, a total of ten participants withdrew during the initial training as they found the stimulation uncomfortable.[35] Reasons for other withdrawals from the study were not requested for ethical reasons but some were volunteered, such as insufficient time to complete the study or because they were planning to be away during the period of the trial and could not commit to participation [*personal communication with Stephen Jackson from Neupulse*].

*Intervention completion*

In the two ORBIT studies, treatment completion was defined as completion of at least the first four child chapters. As such, in the UK study, 88.4% of the intervention group and 93.8% of the comparator group were classed as treatment completers.[33] In the Swedish study, 100% of the intervention group and 94.6% of the comparator group were treatment completers.[37]

*Evidence gap: Although there were statistically significant improvements in YGTSS-TTSS scores over time in the intervention groups as compared to the control groups, changes in the secondary outcomes reported and quality of life scores were less consistent. In particular, the YGTSS-Impairment scores did not show any improvement. Therefore, it is unclear if improvements in tic severity scores translate into improvements in people's daily lives.*

*Evidence gap: Published evidence was not available for all outcomes specified in the scope, namely, behavioural outcomes, functional outcomes, suicidal thoughts and behaviour, and information about digital technology. Clinical measures were reported by all three included studies, albeit using various outcomes and time points, precluding a more extensive pooling of outcomes.*

**Table 10 Summary of reporting of outcomes specified in scope**

| Outcome specified in scope | Study/ies in which reported |
|---|---|
| **Intermediate outcomes** | |
| Intervention-related adverse events | ORBIT UK,[33] ORBIT Sweden[37] |
| Treatment satisfaction and engagement | ORBIT UK,[33] ORBIT Sweden[37] |
| Intervention adherence,<br>rates of attrition and<br>completion | ORBIT Sweden[37]<br>ORBIT UK,[33] ORBIT Sweden,[37] Neupulse[35]<br>ORBIT UK,[33] ORBIT Sweden[37] |
| **Clinical outcome measures** | |
| Measures of symptom severity (self, parental or practitioner reported) | ORBIT UK,[33] ORBIT Sweden,[37] Neupulse[35] |
| Social,<br>behavioural, and<br>functional outcomes | ORBIT UK[33]<br>Not reported<br>Not reported |
| Suicidal thoughts and behaviour | Not reported |
| **Patient-reported outcome measures** | |
| Health-related quality of life | ORBIT UK,[33] ORBIT Sweden,[37] Neupulse[35] |
| Patient's experience and patient's satisfaction | ORBIT UK,[33] ORBIT Sweden[37] |
| Rates and reasons for attrition | ORBIT UK,[33] ORBIT Sweden,[37] Neupulse[35] |
| **Digital technology information** | Not reported |

**Relevant subgroups**

There were insufficient data available to conduct statistical analyses of the specified subgroups. The UK ORBIT study conducted an unplanned post-hoc analysis of the effect of the intervention on the primary outcome by common co-morbidities (anxiety disorder, ADHD). The number of participants with ADHD in each intervention group was 22 while the number of participants without ADHD in the ERP group and psychoeducation group were 79 and 78, respectively. The number of participants with anxiety disorder in the ERP group and psychoeducation group was 30 and 23, respectively, and that without anxiety disorder was 71

and 77, respectively. There was no difference in the effect of the intervention on participants with or without ADHD (p=0.906) or anxiety disorder (p=0.204).

The Swedish ORBIT study conducted post-hoc analyses on the impact of age and sex on the primary outcome. The median age of 11 years was used to split the sample; in the 9-11 years age group there were 124 participants and there were 97 participants in the 12-17 years group. There was an interaction effect between group (ERP and comparator) and time (baseline to 3-month follow-up) on the older group (coefficient [95%CI] -1.21 [-2.14, -0.02]; p=0.05) but not the younger group. More participants in the older group responded to ERP (n=26; 51%) than the comparator (n=10; 23%). The equivalent analysis in the younger group showed no difference between the groups. The sample was also split by gender, with 152 boys and 68 girls (and one participant not included in the analysis due to identifying as non-binary). There was a significant interaction effect for boys (coefficient [95%CI] -1.06 [-2.09, -0.03]; p=0.04) but not for girls. Significantly more boys responded to ERP (n=35; 51%) than the comparator (n=21; 26%) at the 3-month follow-up (OR 2.94 [95%CI 1.48, 5.84]; p=0.002). The equivalent analysis among girls showed no between-group difference.

**Meta-analysis: YGTSS-TTSS**

The two ORBIT trials at low risk of bias reported YGTSS-TTSS scores at 3 and 12 months and were combined in a meta-analysis.[33, 37] The Neupulse study was not included in the meta-analyses as it is a different type of technology than ORBIT. Furthermore, the Neupulse study used sham stimulation and waitlist as comparator interventions whereas the ORBIT studies used psychoeducation as the comparator intervention. The Swedish ORBIT study did not report comparison data at 6 months and, therefore, a meta-analysis at that time point was not possible.[37] Figures 4 and 5 show that the TTSS scores of the YGTSS were significantly lower for the ERP group as compared to the psychoeducation group at 3 months (mean difference -2.12, 95% CI -3.52, -0.73, p=0.0003) and 12 months (mean difference -2.45, 95% CI -4.05, -0.85, p=0.0003). In both meta-analyses, there was no evidence of heterogeneity between studies ($I^2$=0%).

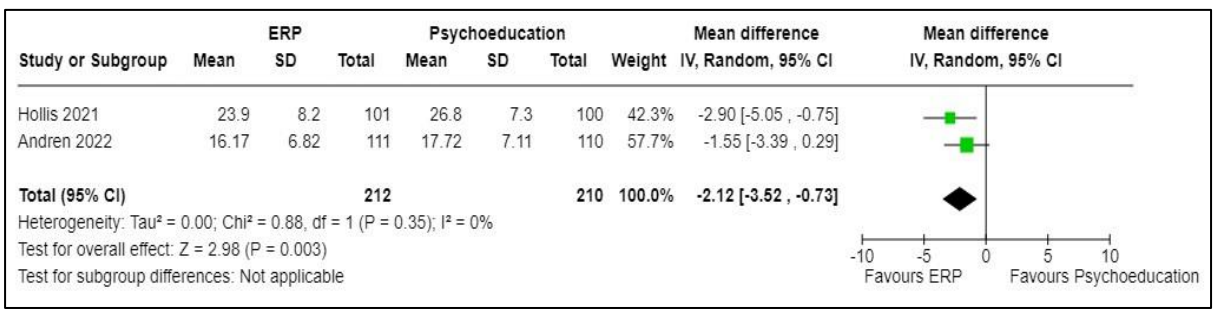

**Figure 4 Meta-analysis for YGTSS-TTSS at 3 months**

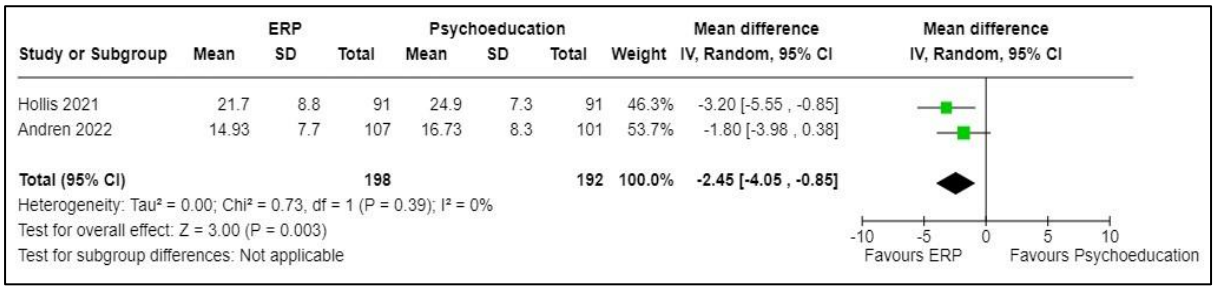


**Figure 5 Meta-analysis for YGTSS-TTSS at 12 months**

**Meta-analysis: YGTSS-Impairment**

The mean difference in the impairment score of the YGTSS at 3 months and 12 months were pooled from the same two ORBIT trials. The YGTSS-Impairment score indicates whether the presence of tic disorders had a negative impact on people's personal life. The YGTSS-Impairment summary score was lower for the ERP group as compared to the psychoeducation group at 3 months (mean difference -1.53, 95% CI -3.32, 0.26, p=0.09) and 12 months (mean difference -0.90, 95% CI -3.90, 2.10, p=0.56) but the differences were not statistically significant (see Figures 6 and 7). There was no evidence of heterogeneity between studies in the 3-month meta-analysis ($I^2$=0%) and a moderate degree of heterogeneity ($I^2$=57%) in the 12-month meta-analysis. The Swedish ORBIT study did not report comparison data at 6 months and, therefore, a meta-analysis at that time point was not possible.[37]

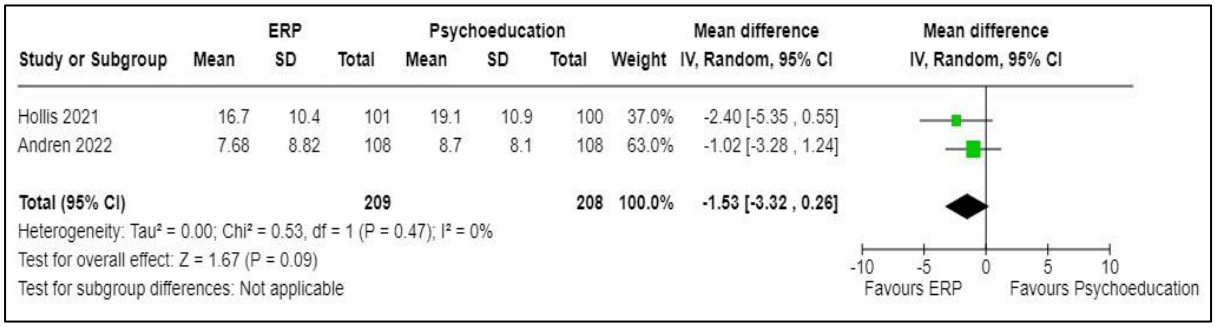

**Figure 6 Meta-analysis for YGTSS-Impairment at 3 months**

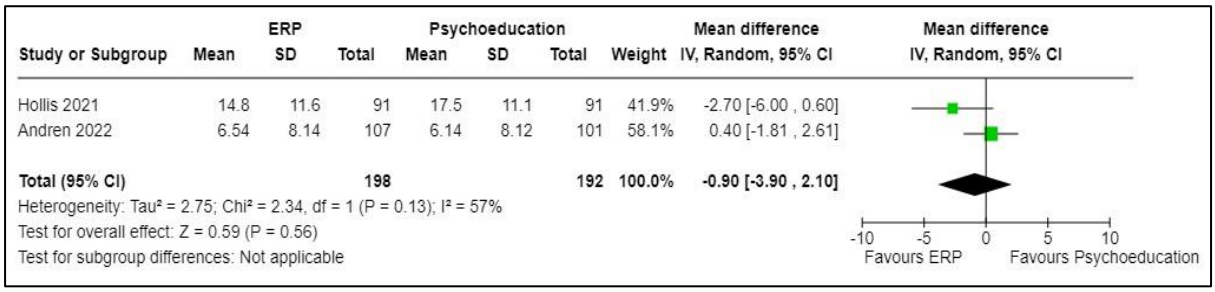


**Figure 7 Meta-analysis for YGTSS-Impairment at 12 months**

**Summary of clinical effectiveness section**

A total of three RCTs investigating two types of digitally enabled therapy, namely ORBIT and Neupulse, for chronic tic disorders and Tourette Syndrome in children, young people and adults were included in the review of clinical effectiveness. Meta-analysis results of the two ORBIT studies showed that tic severity in terms of YGTSS-TTSS scores was significantly lower in children and young people in the ERP groups than those in the psychoeducation groups at 3 months and 12 months. However, no significant improvements in tic-related impairment and distress measured using the impairment score of the YGTSS were observed between treatment groups. In each ORBIT study, secondary clinical outcome measures such as the CGAS, the CGI-I, and the CGI-S did not show a consistently greater response in the ERP group compared to the psychoeducation group at all assessed time points. In the UK ORBIT study, CGI-I showed a greater response in the ERP group at 3, 12 and 18 months but not at 6 months. In the Swedish ORBIT study, CGI-S showed a difference in favour of the ERP group at 3 months, but not at 6 months. In both studies, the CGAS showed no differences between intervention groups at 3 months and a positive difference in favour of the ERP group at 12 and 18 months in the UK ORBIT study. The estimated mean difference in the Parent Tic Questionnaire favoured the ERP group in the UK ORBIT study at 3, 6 and 12 months but not at 18 months and was not significant at 3 and 12 months in the Swedish ORBIT study. Similarly, in the UK ORBIT study, other measures evaluating anxiety and mood, emotional, and behavioural functioning did not show a consistent pattern of response at all assessed time points.

The Neupulse study reported statistically significant lower YGTSS-TTSS scores at 4 weeks in the active stimulation group compared to the sham stimulation group. Greater reductions in YGTSS motor and phonic scores were also observed among participants receiving active stimulation than among those receiving sham stimulation. No significant differences between

treatment groups were observed for the YGTSS-Impairment score or the PUTS-R. In general, participants' engagement with the interventions was reported to be good.

## Assessment of cost-effectiveness

### Review of existing economic model evaluations

#### *Methods for systematic review of economic evaluations*

The initial protocol sought to conduct a systematic search to identify full economic evaluations of digitally enabled therapies for people with tic disorders. Given the lack of anticipated evidence, searches were expanded to include full economic evaluations of any intervention for people with tic disorders. The following databases were searched, with no time, language, or publication type restriction:

- Ovid MEDLINE
- Ovid EMBASE
- Ovid PsycInfo
- NHS Economic Evaluations Database
- International HTA Database (INAHTA)
- Proquest EconLitCost-Effectiveness Analysis (CEA) Registry

Detailed search strategies are provided in Appendix 1. The websites of relevant professional organisations (e.g., ISPOR Scientific Presentations Database) and health technology agencies such as NICE, CADTH, PBAC, ICER and others, were screened for supplementary reports. Reference lists of all incorporated studies were manually reviewed to identify additional relevant studies. Additional data and information provided by the companies was assessed for relevance to the decision problem and included in results summaries where appropriate.

The review included full economic evaluations of any intervention for people with tic disorders. For the purposes of the review, full economic evaluations are defined as comparative analyses of costs and outcomes within the framework of cost-utility, cost-effectiveness, cost-benefit, or cost-minimisation analyses. Economic evaluations conducted alongside single effectiveness studies or decision analysis models were included.

The key findings from included economic evaluations were summarised in tabular format and narratively synthesised. All included studies were appraised with respect to the NICE reference case checklist for economic evaluations.[42] Reporting quality of studies was assessed using the Consolidated Health Economic Evaluation Reporting (CHEERS)[43] checklist and any decision models were quality assessed using the Philips et al. (2004) checklist.[44]

***Results for systematic review of economic evaluations***

The search identified 1242 potentially relevant articles. One further study was provided by one of the companies post search date, leading to a total number of articles of 1243.[40] An initial screen by the study information specialist excluded 1171 clearly irrelevant titles and abstracts, and duplicates. The remaining 72 abstracts were reviewed by a health economist reviewer (DB), of which 10 were retained for full text screening. The final list of studies included 4 publications describing 3 studies.[40, 45-47] Further details of the screening results are provided in the PRISMA flow chart in Figure 8.[48]

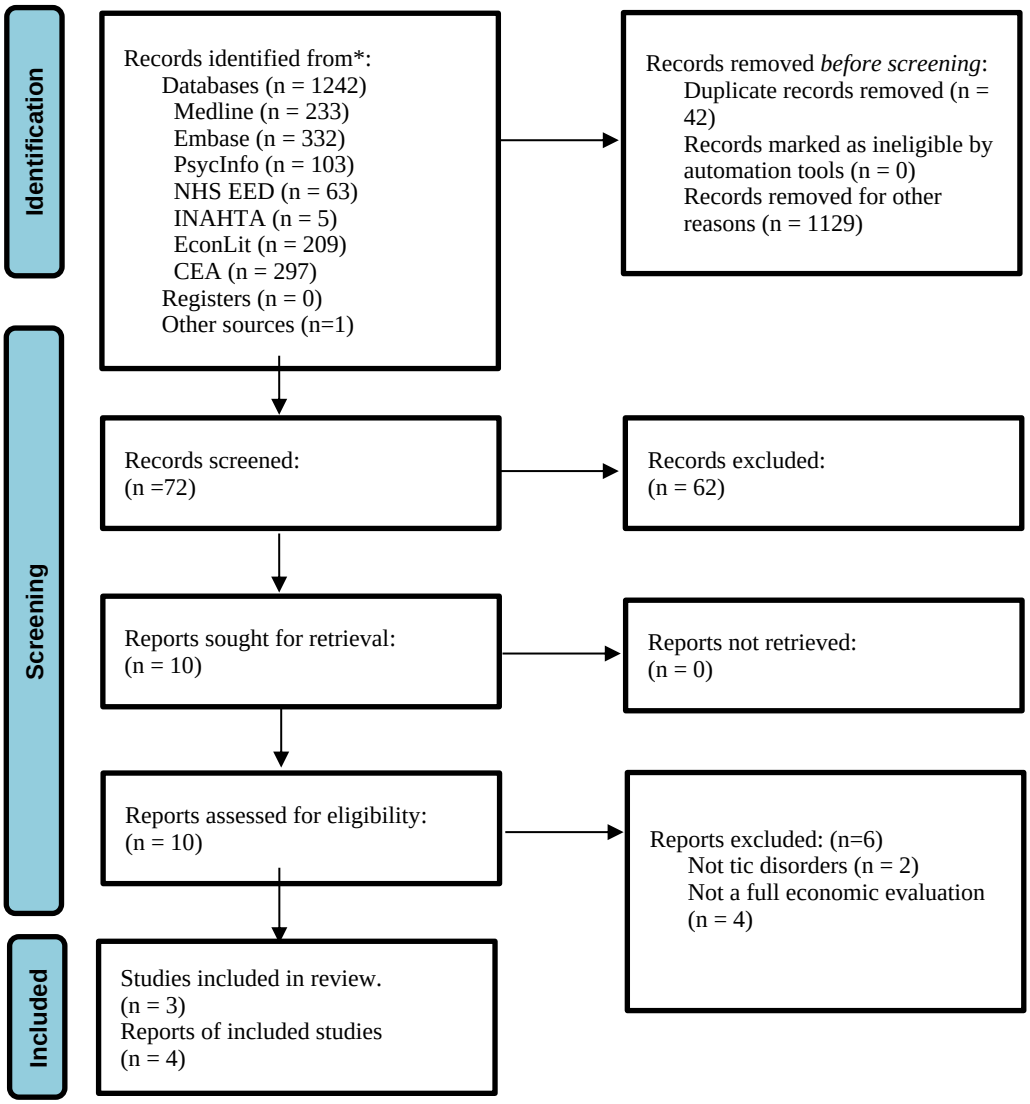


**Figure 8 PRISMA flow chart for economic evaluation studies**

***Summary of existing systematic review of economic evaluations***

Table 11 and 12 summarise the characteristics and results of the included studies.

**Table 11 Summary characteristics of included economic evaluation studies**

| Study | Population | Country | Setting | Intervention | Comparator | EE Framework | EE type | DM type / health states | Perspective | Time horizon | Discounting |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Andren 2024[40] | Diagnosis of TS or chronic tic disorders, mean age 12.1; 69% Male | Sweden | Research clinic | Therapist supported, internet delivered, ERP | Therapist supported, internet delivered, psychoeducation | CEA; CUA | EE alongside RCT | N/A | Provider; health System; Societal | 12 months | N/A |
| Dang[45] 2019 | Severe TS (undefined); int (N=17): mean age 28, 82% M Comp: mean age 35, 75% M | Australia | NR | Deep brain stimulation | Best medical treatment | CUA | DM based on SES, before and after | Alive Dead | NR, assume Healthcare payer. | 10 years | 5% p.a. |
| Hollis 2023[47] | Moderate / severe tic disorder (TS or CTD); mean age 12, 79%M | UK | CAMHS | Online therapist supported ERP | Online, therapist supported, psychoeducation | CEA, CUA | EE alongside RCT + decision model | Type: Markov cohort model. States: Very mild, mild, moderate, severe, very severe | Health and social care; societal | Trial: 18 M DM: 10 yrs. | 3.5% p.a. |

**Table 12 Summary results of the included economic evaluation studies**

| Study | Currency, year | Incremental costs | Incremental Benefits | Base case ICER | Uncertainty from PSA |
|---|---|---|---|---|---|
| Andren 2024[40] | SEK converted to USD, 2021 | Healthcare:<br>-$84.48 (-$440.20 to +$977.60)<br>Societal:<br>+$127.66 (-$1,061.62 to +$2,562.26) | Treatment response (proportion):<br>+0.051 (-0.085 to +0.187)<br>QALYs:<br>+0.007 (-0.013 to +0.027) | Treatment response (proportion)<br>Dominant (NR)<br>QALYs:<br>Dominant (NR) | ~75% at USD 50,000 (Healthcare perspective) |
| Dang 2019[45] | Multiple cost and year inputs, converted to 2018 AUD for outputs / results | Non rechargeable IPG<br>$64,084 AUD (NR)<br>Rechargeable IPG<br>$29,054 AUD (NR) | Non rechargeable IPG<br>1.83 QALY<br>IPG<br>1.83 QALY | ICER: Non rechargeable IPG<br>$34,959 AUD per QALY gained<br>Rechargeable IPG<br>$15,856 AUD per QALY gained | ~40% - 80% across scenarios @ threshold = AUD 70,000 per QALY |
| Hollis 2023[47] | GBP, 2019/20 | Trial (18M)<br>+£662 (-£59 to £1,384)<br>Decision model (10Y)<br>£70.76 (NR) | Trial (18M)<br>+0.040 (-0.004 to +0.083) QALY<br>Decision model (10Y)<br>+0.009 | Trial:<br>£16,708 per QALY gained<br>Model:<br>£8,276 per QALY gained | Trial (base case)<br>~65% @ £20K<br>~79% @ £30K<br>Model:<br>~50% @ £10,000 threshold<br>~60% @ £30,000 threshold |

The quality assessment of the included studies is summarised in Table 13. Full details of quality assessment scores for decision modelling studies against the Philips checklist are presented in Appendix 3.

**Table 13 Summary of quality assessment of the included economic evaluation studies**

| Study | EAG interpretation of relevance against NICE reference case and scope for this assessment | Assessment against Phillips criteria for decision modelling studies |
|---|---|---|
| Andren 2024[40] | **Moderate**, relevant interventions (ERP), in a Swedish setting, but does not explore long-term costs and consequences. | **Not applicable** |
| Dang 2019[45] | **Not applicable.** Intervention and comparators do not meet the scope, does not explore long-term outcomes. Included for completeness from literature review. | **Not applicable** |
| Hollis 2023 (a);[47] Hollis 2023 (b)[46] | **High**. Detailed assessment of relevant intervention and includes a decision analysis model with an appropriate model structure parameterised using trial data from a UK NHS perspective. Note that the comparator may not necessarily reflect UK clinical practice. | **Moderate.** Well conducted study, with appropriate parameterisation using clinical data. Further scenario analyses and discussion around long-term extrapolation assumptions and intervention costing would have been helpful. |

**Economic model overview**

A Markov cohort model was constructed in TreeAge Pro 2023 software (TreeAge Software, Inc., Williamstown, MA, USA) to assess the expected costs and Quality Adjusted Life Years (QALYs) of different treatments for managing tics and Tourette's syndrome in children and young adults. Model outputs are used to calculate the expected net monetary benefit (NMB) for each strategy at a range of cost-effectiveness thresholds. As demonstrated in the review of economic evaluation studies, there were few examples of cost-effectiveness models for tic disorders and the model structure was therefore based on the model developed alongside the recently published randomised controlled trial (RCT) by Hollis et al., which compared online ERP with online psychoeducation for tics in children.[46] Two separate comparisons of cost-effectiveness are presented in this chapter:

1) Online exposure and response prevention (ERP) therapy compared to online psychoeducation in children and adolescents. Despite some uncertainties in modelled parameters, the EAG is satisfied that the evidence base on cost-effectiveness for ORBIT is sufficient to enable decision making. It should however be noted that the online psychoeducation comparator does not align directly with the NICE scope. The EAG found insufficient evidence to enable a comparison of ERP (ORBIT) against face-to-face psychoeducation and this is a key gap in the evidence base that requires further research.

2) Neupulse stimulation compared to a waitlist control (i.e. no stimulation) in young adults. The EAG note that there is no evidence regarding the cost-effectiveness of Neupulse. The only existing clinical evidence (transition probabilities) to populate the economic model comes from short-term (4-week), non-published data that were provided to the EAG through personal communication with the company. The EAG are therefore of the view that there is currently insufficient evidence to decide on the cost-effectiveness case for Neupulse at the moment, and longer-term follow up data is required. Further evidence generation is required to identify medium and long-term trajectory of clinical outcomes, to provide transition probabilities for extrapolation beyond four weeks, and to understand the full costs of intervention delivery and support. The EAG therefore consider the assessment of Neupulse to remain highly uncertain and more appropriate for an early value assessment.

For comparison 1, data are available from the ORBIT study, and this study has been used to replicate the model structure for the current assessment. We use a 5-state Markov model

describing different severity of tics and Tourette's syndrome classified according to quintiles of the YGTSS-TTSS score. An option for an absorbing state of "no tics" is included to explore the impact on results of an assumption that some people may gain complete control of tics and Tourette's syndrome over time, into adulthood, without treatment. The cohort can die from any state during the model according to all cause age and sex adjusted mortality probabilities. There is no excess mortality associated with tics and Tourette's syndrome included in the model.

The cohort can progress through different severity levels of tics in either six-monthly cycles (ORBIT) or 4-weekly cycles (Neupulse), according to a set of transition probabilities obtained from the respective randomised controlled trial data and personal communication with the manufacturer of Neupulse.[35, 46] A range of alternative assumptions are explored to illustrate the impact of different assumptions on tics progression over the longer-term, post treatment, including extrapolation in the longer term based on last observed health state transitions, fixing the cohort in their last observed health state longer term, and switching ERP transitions to the online psychoeducation arm of ORBIT longer term. Intervention cost data are obtained from the literature, though the current price of Neupulse, if it were to be implemented in NHS practice, is not publicly available. Mean CHU-9D based utilities and NHS perspective costs associated with each YGTSS-TTSS defined health state were determined using data reported in the ORBIT study.

In line with the NICE reference case, we take a UK NHS perspective, over a modelled lifetime time horizon. Costs and outcomes accruing beyond the first year were discounted at the recommended rate of 3.5% per year.[49] A summary of the model characteristics is provided in Table 14 below.

**Table 14 Summary of the economic model**

| Factor | Chosen values | Justification |
|---|---|---|
| Time horizon | Lifetime (ORBIT: 88 years for starting age 12; Neupulse: 76 years for starting age 24). Shorter time horizons, 10 years, 5 years and 2 years explored in scenario analyses. | According to NICE guidelines, the time horizon should be extended enough to adequately capture all important differences in costs and health outcomes.[49]<br><br>The mean age of patients in the ORBIT trial was 12 years (14 at the end of the trial follow up). Therefore, a lifetime time horizon of 88 years (86 years post-trial) is appropriate to capture all costs and outcomes, based on the assumption that all patients will be dead by the age of 100.[33]<br><br>Shorter time horizons are explored to reduce the impact of highly uncertain long-term extrapolations. |
| Cycle length | ORBIT: 6 months<br><br>Neupulse: 4-weekly | This aligns with the ORBIT trial, where the primary outcome measure (YGTSS-TTSS) was assessed at 6 months. Also aligns with reported transition probabilities and health state costs<br><br>This aligns with the trial, where the primary outcome measure (YGTSS-TTSS) was assessed at 4 weeks and transition probabilities were provided up to 4-weeks only.[35] |
| Intervention(s) | • ORBIT (MindTech)<br>• Neupulse (Neurotherapeutics) | This aligns with the NICE final scope. |
| Comparators | • ORBIT: Standard care represented as online psychoeducation (ORBIT)<br>• Neupulse: wait list control, no intervention | The comparators differ to the NICE scope, which stated psychoeducation, delivered in a face-to-face format was the ideal comparator. However, the EAG were unable to find any evidence comparing the interventions to face-to-face psychoeducation and definitions of psychoeducation across other studies were too heterogeneous to enable any form of indirect comparison to be performed. |
| Discount rate for costs and outcomes | 3.5% | This aligns with the NICE reference case.[49] |

| Factor | Chosen values | Justification |
|---|---|---|
| Perspective | UK NHS and PSS | This aligns with the NICE reference case, which considers all direct health effects for patients and, carers (if applicable).[49] |
| Half-cycle correction | A half cycle correction was applied to all modelled costs and outcomes. | Aligns with best practice modelling methods. |
| Source of clinical efficacy | ORBIT study informed the clinical efficacy for online therapist-supported exposure and response prevention (ERP) and online psychoeducation up to 18 months.<br><br>Neupulse study informed the clinical efficacy for active Neupulse stimulation, and waitlist (no stimulation) up to 4-weeks. Transition probabilities provided through personal communication with the company.<br><br>Long-term effectiveness of all interventions is unknown | Head-to-head data for online ERP and online psychoeducation is informed by transition matrices published in the ORBIT trial.[46]<br><br>Data for Neupulse obtained from company upon request because published data on transition probabilities were not available from the published literature in a manner suitable for informing the economic model structure. |
| Source of utilities | Parent proxy reported responses to the CHU9D, obtained from the ORBIT study, applied to all modelled health states, regardless of age. Assumed that utility of very mild and mild states was equivalent. Assumed that utility of severe and very severe states was equivalent. All HSUVs age and sex adjusted to UK general population norms (based on EQ-5D general population utilities). | These were the only HSUVs available from the literature. Children self-reported responses to the CHU-9D in the study but parent proxy reports were used to calculate HSUVs. CHU-9D utilities were applied into adulthood for all health states because of a lack of data from adult generic HRQoL measures for tics and Tourettes.[46] An assumption about equivalence between mild / very mild states and severe / very severe states was required due to a lack of data. |
| Source of costs | • Intervention costs, including BIP platform costs and therapist support costs for ORBIT and online psychoeducation obtained from the ORBIT study.<br>• Neupulse intervention costs obtained from personal communication with company, including upfront device cost and monthly software subscription costs. Personal communication with the company suggested [redacted] | ORBIT study provides the best available costing information for the intervention. It was not possible to re-cost all aspects of the intervention as sufficient information to do this was not available from the source study, therefore costs were inflated to current prices instead. Variation in intervention delivery costs, particularly whether ongoing costs of the BIP platform are required in either or both model arms for the ORBIT comparison. Scenario analyses explore the impact of different throughput values on the platform to determine the impact on average per person costs. |

| Factor | Chosen values | Justification |
|---|---|---|
| | • Health state costs obtained from the ORBIT study, validated with clinical experts.<br>• All costs were adjusted to 2023 values using the UK NHS Cost Inflation Index (NHSCII), available from https://kar.kent.ac.uk/105685 | |
| Outcomes | • Total costs<br>• Incremental costs<br>• Total QALYs<br>• Incremental QALYs<br>• ICERs | Consistent with the final NICE scope and the NICE reference case. |
| Uncertainty | • Univariate sensitivity analysis<br>• Scenario analysis<br>• Probabilistic sensitivity analysis<br>• Evidence gaps highlighted in italics throughout the chapter. | Consistent with NICE reference case. A particular focus is placed on scenario, 2-way scenario analyses, probabilistic and highlighting of evidence gaps to inform key priorities for future research questions. |

**Abbreviations:** NICE, National Institute for Health and Care Excellence; YGTSS-TTSS, Yale Global Tic Severity Scale Total Tic Severity Score; EAG, External Assessment Group, UK NHS and PSS, United Kingdom National Health Service and Personal Social Services; ERP, Exposure, and response prevention; CHU9D, Child Health Utility 9D; HRQoL, Health-related quality of life; BIP, Barninternetprojektet (Child Internet Project; Swedish digital platform); NHSCII, National Health Service Cost Inflation Index; QALY, Quality-adjusted life-year; ICER, Incremental cost-effectiveness ratio; EVPI, Expected value of perfect information

**Model structure**

After conducting a rapid literature review of existing economic evaluations of any intervention, in any population for chronic tic disorders or TS, we identified one published Markov decision analytic model that extended the analysis of cost-effectiveness from the ORBIT trial for treating tics in children aged 9 to 17-years.[47] Full details of the ORBIT trial are provided in Table 3 above, with results of the clinical effectiveness outcomes detailed in Tables 4, 6 and 8. As the ORBIT study model was the only decision modelling study that closely meets the scope for this project, we have built the current model structure around the health states defined in that study. The EAG's clinical expert advisor confirmed that the model structure from the ORBIT was appropriate for decision making as it captured disease severity using the most used outcome measure for patients with tics and TS, the YGTSS score. The Markov cohort model structure is illustrated in Figure 9.

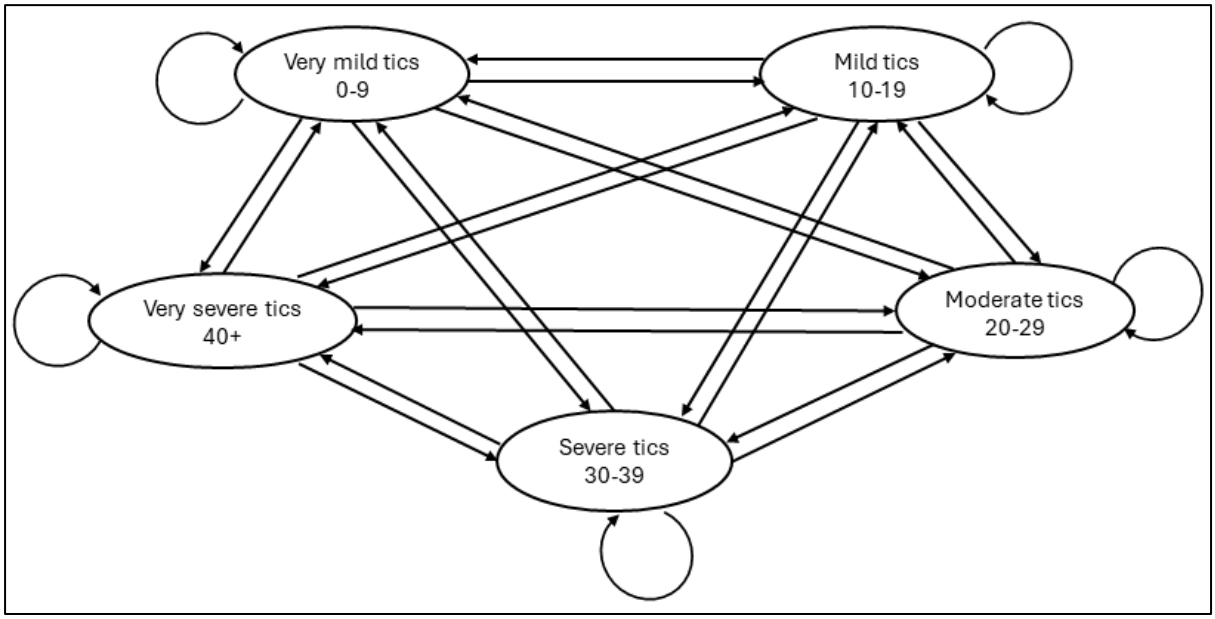


**Figure 9 Schematic diagram of the Markov model structure of the economic model**

The model comprises five mutually exclusive health states that describe the severity of tics and TS, defined as quintiles of the YGTSS-TGSS score as depicted in the schematic above. The cohort can move through the model states, according to a set of transition probabilities that allow for progression, stability, or regression of symptoms in each model cycle. Two different cycle lengths are considered depending on the comparison being evaluated: a six-month cycle length for ORBIT and a four-week cycle length for Neupulse. The four-weekly cycle length was required for Neupulse due to it being the only available data. Cycle-lengths were chosen given the limited availability of data, especially for Neupulse.

Health states are defined according to the level of tic severity as measured using the Yale Global Tic Severity Scale (YGTSS), Total Tic Severity Score (TTSS). [50] The classification was based on the severity structure proposed by Bloch and Leckman, which was also applied in the ORBIT modelling, where tics are classified according to quintiles of the TTSS on the YGTSS: very mild (0-9), mild (10-19), moderate (20-29), severe (30-39), and very severe (40-50).[9] An additional, semi-absorbing, tics-free health state was considered for scenario analysis. The purpose of the scenario analysis was to allow for a proportion of patients to become permanently tics-free over time, into adulthood. However, based on clinical expert advice, this was not considered appropriate for the base case analysis. Definitions of each health state are summarised in Table 15.

**Table 15 Health states categorised using TTSS on the YGTSS**

| Health states | YGTSS-TTSS |
|---|---|
| No tics (completely tic free), scenario analysis only | 0 |
| Very mild | 0-9 |
| Mild | 10-19 |
| Moderate | 20-29 |
| Severe | 30-39 |
| Very severe | 40-50 |

**Abbreviations:** TTSS, Total Tic Severity Score; YGTSS, Yale Global Tic Severity Scale; YGTSS-TTSS, Yale Global Tic Severity Scale Total Tic Severity Score

In each model cycle, the cohort are also exposed to a risk of all-cause mortality where they enter the "death" state from any other model state. Death is an absorbing state in the model, based on age-specific mortality rates reported for males and females in the UK life tables.[51]

*An important evidence gap relating to the model structure is that the long-term potential for people with chronic tic disorders or TS to become tic-free over time, into adulthood is unclear. Scenario analyses explore the potential for this based on one small study, but caution is required regarding heterogeneity in the underlying severity of that study compared to the studies included in our review.*

**Population**

The modelled populations were different for comparison 1 (ORBIT) and comparison 2 (Neupulse). This reflects the likely different populations in which these treatments would be used in UK clinical practice (e.g. Neupulse in an older population and with more severe tics

and TS). The modelled starting cohort's characteristics are therefore obtained from the key clinical trials of both interventions as described below.

***ORBIT***

The population entering the model for ORBIT and online psychoeducation consists of children and young people, diagnosed with chronic tic disorders who continue to report bothersome tics after initial psychoeducation, which is in line with the NICE scope.[52] The specific participant characteristics were obtained as the mean age and gender proportion across the full study population in the ORBIT trial. The detailed proportion of participants starting in each severity health state undergoing online ERP and psychoeducation treatment was based on data from the ORBIT trial. Most participants entered the model in the moderate, severe or very severe states, with comparatively fewer starting with mild or very mild tics according to the YGTSS.

***Neupulse***

For Neupulse, the population is restricted to individuals aged 12 and older with confirmed or suspected TS and chronic tic disorder, with moderate to severe tics. The starting population in the model for the Neupulse and waiting list control arms of the model was therefore based on the mean characteristics across the Neupulse and waitlist control groups from the Maiquez, 2023 trial.[35] The Neupulse trial included participants with comparatively more severe tics and TS and significantly higher YGTSS-TGSS score compared to the ORBIT trial population. This necessitated separate comparisons of different populations for cost-effectiveness analysis. Data for the distribution of the cohort starting in each modelled state at baseline were not available from the published literature. Starting proportions according to our modelled definitions were provided through personal communication with a co-author from the Maiquez study *(Personal communication, Neupulse, May 2024).* Modelled population characteristics for both comparisons are summarised in Table 16.

*A key evidence gap for the Neupulse comparison relates to a lack of available data in the public domain regarding the starting distribution of the cohort across Markov model states. However, information was helpfully provided by the company. It was not possible to conduct a fully incremental analysis, including a comparison or Neupulse with ORBIT as the clinical trials were conducted in different population groups. Importantly, there was no evidence to enable a cost-effectiveness assessment of any of the interventions compared to current UK standard of care, as defined in the NICE scope (online / face-to-face psychoeducation). The online psychoeducation arm of ORBIT uses the BiP platform and may therefore be a more*

*active comparator than current UK clinical practice. Due to the lack of available data, the assessment therefore relies on the comparisons considered in the key clinical trials.*

**Table 16 Modelled population characteristics for ORBIT and Neupulse evaluations**

| | **ORBIT** | | **Neupulse** | | **Distribution** |
|---|---|---|---|---|---|
| | **Psychoeducation** | **ERP** | **Active simulation** | **Waitlist** | |
| **Participant demographics** | | | | | |
| Mean Age | 12 | | 24 | | Fixed |
| Proportion male | N=177/224 (79%) | | Active: N= 26/41 (63%)<br>Waitlist: N= 26/41 (63%) | | Fixed |
| **Disease severity (model health state starting proportions (i.e. reported at 18 months ORBIT trial follow-up)** | | | | | |
| | **%** | **Alpha** | **%** | **Alpha** | **%** | **Alpha** | **%** | **Alpha** | |
| Very mild | 4% | 4 | 12% | 11 | 0 | 0 | 0 | 0 | DT |
| Mild | 18% | 16 | 19% | 17 | 0 | 0 | 3% | 1 | DT |
| Moderate | 37% | 33 | 33% | 29 | 11% | 4 | 6% | 2 | DT |
| Severe | 21% | 19 | 14% | 12 | 18% | 7 | 43% | 15 | DT |
| Very severe | 20% | 18 | 22% | 20 | 71% | 27 | 49% | 17 | DT |
| No tics | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Abbreviations:** ERP, Exposure and response prevention; DT, Dirichlet distribution

### Perspective, time horizon and discounting

The base case analysis reports incremental cost per QALY gained over a lifetime time horizon (up until age 100) from a UK NHS and personal social services (PSS) perspective. All costs and QALYs beyond 12 months were discounted at a rate of 3.5% per year in line with the NICE reference case.[49] Shorter time horizons (2, 5 and 10 years) are explored in scenario analyses to reduce the uncertainty associated with longer-term tics and TS progression. For the ORBIT comparison, the model starting point is 18 months, as the model includes the costs and QALY payoffs reported in the clinical trial up to 18 months follow-up. Discounting formulae are adjusted accordingly. A 2-year time horizon therefore refers to 18 months plus 2 years of extrapolation for the ORBIT comparison. No cost-effectiveness trial data are available for the Neupulse; therefore, the model is started at time zero.

*A key evidence gap relates to long-term extrapolations beyond 18 months for the ORBIT comparison and beyond 4 weeks for the Neupulse comparison. This is a significant source of*

*uncertainty, and it may therefore be appropriate to consider shorter time horizons given the lack of robust long-term data on tic / TS progression with and without treatment.*

**Model Parameters - Transition probabilities**

***Transition probabilities based on observed data.***

For the ORBIT study, costs and QALYs from the trial are used directly within the economic model as payoffs up to 18 months (first 3 model cycles). The starting proportions for the Markov cohort were taken as the distribution of health state occupancy at the end of the ORBIT study follow-up at 18 months. Beyond that time point, baseline transition probabilities were derived from the online psychoeducation arm of the ORBIT trial follow-up, calculated from observed transitions between 6 and 18 months, aiming to assess the natural course of tic progression post-intervention.[33, 46] Specific transitions between 6-12 and 12-18 months were not reported. The calculation of transition probabilities in the ORBIT study excluded transitions between baseline and 6-months to remove the initial steeper improvement in tics in both arms of the trial from the calculation of long-term extrapolation transition probabilities. The six-monthly transitions calculated from the observed data between 6-18 months were applied in the model from cycle 3 onwards in the base case analysis. Transition probabilities for ERP were also obtained directly from the ORBIT study, using a similar approach for data from the intervention arm of the trial.

For Neupulse and waiting list control, a similar approach was taken to deriving transition probabilities. There was no trial-specific cost or QALY data were available to inform the model, therefore the starting point for the cohort was time zero. Transition probabilities were not available from the published literature. Instead, 4-week transitions were obtained through personal communication with the company. The EAG provided a pre-specified transition matrix form, in which count data from the study were entered and returned to the EAG for use in the model.

All transition probabilities are incorporated into the model using Dirichlet distributions using alpha values reflecting transition counts back calculated from transition probabilities reported in Table 17 of the ORBIT NIHR report, assumed to reflect six-monthly transitions, though it is not explicitly stated in the report how these were derived. For Neupulse, the Dirichlet distributions are parameterised using 4 weekly alpha counts provided through personal communication with the company. Data underpinning these distributions are provided in Table 17.

**Table 17 Transition probabilities [reproduced from Hollis et al., 2023, Table 17]**

| | To very mild | To mild | To moderate | To severe | To very severe | n |
|---|---|---|---|---|---|---|
| **Six monthly transition probabilities for ORBIT and online psychoeducation** | | | | | | |
| ***Online psychoeducation*** | | | | | | |
| From very mild | 0.500 | 0.500 | 0.000 | 0.000 | 0.000 | 4 |
| From mild | 0.074 | 0.817 | 0.036 | 0.036 | 0.036 | 16 |
| From moderate | 0.019 | 0.060 | 0.827 | 0.092 | 0.000 | 33 |
| From severe | 0.000 | 0.051 | 0.134 | 0.680 | 0.134 | 19 |
| From very severe | 0.000 | 0.000 | 0.021 | 0.115 | 0.863 | 18 |
| ***Online ERP*** | | | | | | |
| From very mild | 0.788 | 0.105 | 0.105 | 0.000 | 0.000 | 11 |
| From mild | 0.147 | 0.609 | 0.174 | 0.022 | 0.046 | 17 |
| From moderate | 0.011 | 0.150 | 0.754 | 0.035 | 0.047 | 29 |
| From severe | 0.000 | 0.000 | 0.113 | 0.886 | 0.000 | 12 |
| From very severe | 0.000 | 0.021 | 0.044 | 0.021 | 0.912 | 20 |
| **Four-weekly cycle specific transition probabilities for Neupulse and waiting list control** | | | | | | |
| ***Active Neupulse stimulation*** | | | | | | |
| From very mild | 1[A] | 0.00 | 0.00 | 0.00 | 0.00 | 0 |
| From mild | 0.00 | 1[A] | 0.00 | 0.00 | 0.00 | 0 |
| From moderate | 0.00 | 0.50 | 0.25 | 0.25 | 0.00 | 4 |
| From severe | 0.00 | 0.00 | 0.14 | 0.86 | 0.00 | 7 |
| From very severe | 0.04 | 0.00 | 0.11 | 0.33 | 0.52 | 27 |
| ***Waitlist (no stimulation)*** | | | | | | |
| From very mild | 1[A] | 0.00 | 0.00 | 0.00 | 0.00 | 0 |
| From mild | 0.00 | 0.00 | 1.00 | 0.00 | 0.00 | 1 |
| From moderate | 0.00 | 0.00 | 1.00 | 0.00 | 0.00 | 2 |
| From severe | 0.00 | 0.00 | 0.13 | 0.60 | 0.27 | 15 |
| From very severe | 0.00 | 0.00 | 0.00 | 0.29 | 0.71 | 17 |

**Abbreviations:** ERP, Exposure and response prevention

[A] Where no data were available for any given transition out of a health state, it was assumed that people remained in that state if they entered the state in subsequent model cycles.

*Evidence gaps*: *It should be noted that Neupulse transition probabilities were not available from the published literature and were instead sourced through personal communication with the company. Data were provided up to 4 weeks, which the EAG considers a short time horizon. These data are insufficient to make any strong predictions of longer-term outcomes*

*and clinical effectiveness data up to six months, anticipated to be published in future, will help reduce the uncertainty somewhat. Transition probabilities for all comparisons (ORBIT and Neupulse), are derived from very small counts. This leads to substantial uncertainty regarding treatment effect sizes in the longer-term. For example, transition probabilities derived from less than 10 observations should be interpreted particularly cautiously as they may lead to misleading deterministic base case results. Larger studies of the interventions are required, with longer-term follow-up, particularly for Neupulse required to improve modelling projections.*

***Transition probabilities to the absorbing 'tics free' state in scenario analyses***

Inclusion of a semi-absorbing state of 'tics free' is explored in a scenario analysis. The intention of this state is to model a proportion of people who may 'grow out' of tics in the longer term, returning to a quality of life assumed equal to that of the general population. The proportion of the cohort entering the absorbing 'tics free' state in the scenario analysis is derived from a study reporting that, over one-third (37%) of a combined sample of across two studies of N=82 children with TS were completely tic-free. We use the median follow-up from Bloch et al., of 7.3 years to fit an exponential distribution to the median to determine a linear progression into the tics free state over time for this scenario analysis.[9]

Since cycle specific transitions into the tics-free state were unavailable, we used an exponential formula based on the median time to an event to estimate the proportion of individuals who become tic-free in each six-monthly cycle. Transitions to the tic-free state were applied from each modelled tic-severity state at an equal rate due to a lack of evidence to support a tic severity adjustment.

The cycle-specific transition into the tics-free state was calculated as:

$$P(t) = \exp(\ln(0.5)/\text{median number of cycles} \times \text{current cycle})$$

Where:

- P(t) is the probability of being disease-free at time t.
- ln is the natural logarithm.
- 0.5 represents the 50th percentile (median).
- The median number of cycles is the time at which 50% of the cohort remains disease-free.
- The current cycle is the specific time point for which we are calculating the probability.

*Evidence gap: The long-term trajectory towards a tic-free state, i.e. the potential for people to have completely resolved tics over time, into adulthood is not well understood. There appears to be limited long-term data, and it is unclear how the time to achieve tics-free would depend on the underlying severity of chronic tics of TS. Further evidence is required to better inform modelling of any potential possibility for transition to a tics-free state over time and whether different intervention types might have differential impacts on these outcomes. Our simplistic scenario analysis assumes that transitions occur at the same rate from any state of the model. This assumption is likely to lack face validity, given that people become tics gradually over time. However, in the absence of alternative data, this was deemed the most appropriate approach in which to conduct the scenario analysis.*

***Longer-term transition probabilities beyond the end of the observed period from trial data***

The EAG note that there is significant uncertainty and a lack of data to describe the long-run transitions between model health states beyond the observed periods in the respective trials. The tentative base case analysis is formulated on the assumptions which the EAG consider potentially plausible, and in line with the clinical expert advice we have received, but a range of different assumptions are applied in scenario analyses. For online psychoeducation and ORBIT, we assume that the transition probabilities between 6 and 18 months can be extrapolated over a lifetime horizon. These transitions exclude the initial improvement in both arms seen up to 6 months in the study. We assume that, to achieve these outcomes, ongoing use of the BiP platform would be required in both arms of the model. However, the costs of ongoing therapist support would not be incurred. This assumes that both ERP and online psychoeducation are successful longer-term and that learned behaviours can be implemented indefinitely.

For Neupulse, the mechanism of action is electrical stimulation. It is therefore assumed that the intervention is effective only so long as it is used. For the base case analysis, we assume, similarly, to ORBIT that transition probabilities from 4-weeks can be extrapolated longer-term. Again, this would require that Neupulse treatment is continued indefinitely. However, it may be more appropriate to assume that full effectiveness for Neupulse is achieved at 4-weeks and that ongoing treatment would not lead to further improvement in symptoms, with the cohort instead being held in their observed state at 4-weeks.

All these assumptions are surrounded by considerable uncertainty, and it is not possible to derive a clear base case set of assumptions. For that reason, we have reported several scenario analyses as follows:

- Assuming that longer term transition probabilities switch from the active intervention to comparator transitions beyond the observed time points. This would be a pessimistic assumption for Neupulse. However, it would be optimistic for ORBIT given that there is some evidence that transition probabilities may be favourable to psychoeducation longer term with initial gains potentially being reversed.
- Assuming that each cohort is held in their last observed state for the remainder of the economic model.
- Given that none of these scenarios for long-term modelling are supported by robust evidence and are, at best, speculative, the model time horizon has been reduced to 10, 5 and 2 years in scenario analyses to minimize the impact of long-term extrapolation assumptions on results.

*Evidence gaps: Long-term transition probabilities are unknown for all the interventions. It is unclear how transition probabilities for Neupulse would change beyond the study intervention phase (4-weeks). There is some suggestion that transition probabilities for online psychoeducation may be slightly favourable to psychoeducation longer term suggesting that gains in the ERP arm might not be sustained longer-term. However, all these data are highly uncertain, and it is more appropriate to consider the balance of uncertainty around model outcomes using probabilistic analyses, with the uncertainty captured through small counts informing the Dirichlet distributions of transitions. Future, longer-term follow up studies are required to better understand the long-term impact of interventions on chronic tics and TS.*

**Model parameters - costs and resource use**

***Intervention costs – ORBIT and online psychoeducation***

All cost items for ERP and online psychoeducation were sourced directly from the ORBIT trial. It was not possible to identify each item of resource use in sufficient detail to enable a recalculation of costs using current PSSRU unit costs of staff time. Therefore, costs reported in the ORBIT study are inflated to 2023 values for application in the model. The Neupulse device cost was obtained from the company upon request. A summary of intervention costs, inflated from those reported in the ORBIT study is provided in Table 18. The costs for consideration include:

- The BiP platform costs (fixed cost of setting up platform and variable cost per text sent from the platform, based on usage). The BiP platform was used in both arms of the study in the ORBIT trial, with an assumed throughput for calculation of per

person costs of N=222 (combined sample across both arms of the ORBIT study). However, the ORBIT study only included costs in the ERP arm for their economic modelling. The EAG consider it appropriate to include the costs of the platform in both arms of the study to align the resource use incurred with the benefits derived. The throughput is varied between 100 and 1000 for sensitivity analyses.

- Costs of therapist support time, including a fixed component for training and a variable component of service delivery and patient support.

For the EAG analyses, costs were split into an 'upfront' initial cost, as described above, plus and ongoing cycle-specific cost based on variable cost of platform usage. The ongoing cycle specific costs are applied to both arms in the base case analysis, on the assumption that long-term transition probabilities can only be achieved if use of the platform is continued indefinitely over time. These assumptions are tested in scenario analyses. Full details of the intervention costing are provided in Table 18 below.

*Evidence gaps: The ORBIT study used the BiP platform in both study arms, but costs in the ORBIT economic evaluation only included costs in the ERP arm. The EAG preferred to include the costs in both arms because this reflects the potential resource use incurred in the trial. However, it is unclear how the availability of the BiP platform would have impacted on the effectiveness of the online psychoeducation arm of the study, but it is plausible that it would have over-estimated effectiveness in the comparator arm relative to standard care where the platform was not available. Similarly, the exact throughput for the BiP platform is unclear, and this impacts on costs. For the longer-term extrapolation, the EAG includes some ongoing costs of platform access for the model time horizon because we also extrapolate short term transition probabilities over the longer-term time horizon. However, it is unclear which combination of intervention costs and long-term extrapolations is most appropriate.*

**Table 18 Intervention costs for ORBIT and online psychoeducation**

| *Cost per participant* | Initial up-front costs | | Ongoing costs per cycle | |
|---|---|---|---|---|
| | **Psychoeducation** | **ERP** | **Psychoeducation** | **ERP** |
| Fixed cost of BIP platform per participant [A] | £43.05 | £43.05 | £0 | £0 |
| Fixed cost of Therapist support (training and supervision) [A] | £75.38 | £75.38 | £0 | £0 |
| Variable platform costs [B] | £6.32 | £7.73 | £6.32[C] | £7.73[C] |
| Variable cost of therapist support [B] | £42.76 | £48.38 | £0 | £0 |
| **Total intervention cost** | **£167.51** | **£174.54** | **£6.32** | **£7.73** |
| **Scenario analysis 1, include only variable cost of therapist support for psychoeducation** | **£42.76** | **£174.54** | **£0** | **£7.73** |
| **Scenario analysis 2, apply approach from ORBIT study (include only variable costs of platform and therapist support for psychoeducation and remove all ongoing costs)** | **£49.08** | **£174.54** | **£0** | **£0** |
| **Scenario analysis 3, Only include variable therapist support costs, include ongoing costs + platform throughput (n=100)** | **£42.76** | **£227.06** | **£6.32** | **£7.73** |
| **Scenario analysis 4, Only include variable therapist support costs, include ongoing costs + platform throughput (n=1000)** | **£42.76** | **£141.05** | **£6.32** | **£7.73** |
| **Scenario analysis 5, remove ongoing costs from both arms** | **£167.51** | **£174.54** | **£0** | **£0** |

**Abbreviations:** ERP, Exposure and response prevention; BIP, Barninternetprojektet (Child Internet Project; Swedish digital platform

[A] Fixed platform costs calculated as SEK: 96,000, converted to 2022/23 GBP: £9,556.96 and divided by the assumed throughput on the platform (N=222, combined ORBIT trial sample). The fixed therapist support includes costs of training and supervision, based on weekly one-hour supervision sessions with therapists during 10-week intervention delivery. Total costs divided by total patient numbers in the study (N=222) to obtain per person costs. Costs were reported in Hollis et al., 2021, Table 1. fixed cost of therapist support (Appendix results) and inflated to 2022/23 values for use in the model. [33]

[B] Each time a participant accesses the BIP platform, a text message is sent to them. The average cost of sending a text message across various UK network providers has been calculated in the ORBIT study and multiplied by the number of total system logins per study arm and divided by the sample size to estimate per person costs. A patient-level variable cost of therapist support is also calculated for each participant based on the reported therapist time and the therapist's grade with whom they interacted. Further details available from: Hollis et al., 2021, Table 6 of Appendix results, variable cost. [33]

[C] Costs are per year, adjusted to six-monthly cycles and discounted in model.

***Intervention costs - Neupulse***

The cost for Neupulse consists of two components: an initial cost of [redacted] for purchasing the device with a usable life of [redacted]. The economic model therefore includes this cost every [redacted] for the duration of the model time horizon, on the assumption that the intervention costs will be incurred indefinitely to maintain the intervention's effectiveness. Similarly, a monthly subscription cost of [redacted] is applied in each model cycle. The monthly subscription includes access to an app for controlling the device, daily disposable hydrogel pads, storage of medical data associated with the therapy, and access to both digital and human product support resources. It was assumed that there were no intervention costs assigned to the waiting list control arm of the model and that no additional costs would be incurred associated with training or therapist support as Neupulse is intended as a self-administered device, with all required patient training provided within the company provided materials.

**Table 19 Neupulse intervention costs**

| Cost item | Fixed |
|---|---|
| Neupulse device cost, incurred every [redacted] | [redacted] |
| Subscription cost/month | [redacted] |

*Evidence gap: The costs of Neupulse are not currently publicly available and have been provided to the EAG through personal communication with the company. It is unclear how the costs provided would translate to costs in UK NHS practice if the device was made available to the NHS. However, it is feasible that a combination of factors, including additional costs of sales to the NHS, or reductions due to economies of scale would be relevant, meaning that the cost to the NHS may not be accurately represented by the costs used in the economic modelling. Whilst the company suggest that there are no training or staff costs associated with use of the device, there are, as yet no data to support or refute this assumption.*

***Health state costs***

The EAG's understanding of UK clinical practice is that management of children with tics and TS is most likely to take place in paediatrics, or CAMHs services, with management of adults typically occurring in community mental health teams of neurology clinics. Within the ORBIT study, the authors compared resource use and costs between ERP and online psychoeducation across several different categories of costs (specialist tic services,

community services, hospital services, A&E and medication costs). They found no clear differences between groups for any of the cost categories, despite potential clinical benefits. The authors also explored the impact of tic severity on these cost categories. The only cost category identified as being significantly determined by tic severity was the use of specialist tic services. Therefore, the model used health state costs that were informed by a regression analysis to determine health state specific costs (defined as use of specialist tic services), with adjustment for age, comorbidities using the development and wellbeing assessment (DAWBA), and gender.

The EAG's base case analysis uses the cost data from the trial on the grounds that it is a conservative estimate of the potential cost-savings of moving between different health states but acknowledging that it might not capture the full range of services utilised by patients with chronic tics and TS. The EAG's clinical expert and one response to a survey of specialist committee members for this topic suggested that improvements in tic severity might also reduce the need for medication. The EAG therefore explored a scenario analysis where an additional medication cost was added to the moderate and severe YGTSS health states, but not to the mild / very mild states. Medication usage also likely varies across UK clinical practice, both in terms of the proportion of patients receiving medication and the distribution of medications amongst those who do. For the scenario analysis, the EAG applied six-month costs of Clonidine (assumed 50%) and Haloperidol (assumed 50%) in the moderate state with a cost of Clonidine (45%), Risperidone (10%) and Haloperidol (45%) applied in the severe and very severe tics states. Costs of medications for the scenario analysis were sourced from eMIT 2023 prices as:

- Clonidine 25mcg, dose up to 150 micrograms per day, unit cost £2.95 per pack size of 112 tablets, 10 packs required per 6-month model cycle, cost per cycle: £29.50
- Haloperidol 5mg, dose of up to 5mg per day, unit cost £0.84 per pack size of 28 tablets, 6 packs required per 6-month model cycle, cost per cycle: £5.04
- Risperidone 1mg, average dose of approximately 5mg per day, unit cost £0.77 per pack size of 60 tablets, 16 packs required per 6-month cycle, cost per cycle: £12.32.

Based on the weightings above, an additional cost of £17.27 and £16.78 is added to the severe and very severe tic states respectively.

All cost parameters were incorporated into the model probabilistically using gamma distributions. Where a measure of spread was not available for any of the cost parameters, the SE was assumed to be 10% of the mean. All cost parameters are summarised in Table 20.

*Evidence gap: There is limited evidence external to the clinical trial with regards to the most appropriate health state costs to apply in the economic model. A survey of clinical experts for this assessment failed to provide any additional information to reflect variation in UK clinical practice. The EAG are also aware that many people may not have access to services specifically to treat their tics / TS and that in some cases, these services may be embedded within other services for other co-morbid conditions. Care is required to avoid double counting of health state costs and further research is needed to better understand the care pathways followed by patients with tics and TS in UK clinical practice. Similarly, there are no data from the ORBIT study regarding the health state costs to apply for adults. This is an added uncertainty, particularly for the Neupulse assessment.*

**Table 20 Summary of health state costs applied in the model.**

| Parameters | | Mean | SE | alpha | lambda | Dist. | Source |
|---|---|---|---|---|---|---|---|
| **6-month health state costs** | | | | | | | |
| Very mild | Base case | £145.14 | £17.11 | 71.96 | 0.50 | Gamma | ORBIT |
| | Scenario | £145.14 | £17.11 | 71.96 | 0.50 | Gamma | ORBIT |
| Mild | Base case | £145.14 | £17.11 | 71.96 | 0.50 | Gamma | ORBIT |
| | Scenario | £145.14 | £17.11 | 71.96 | 0.50 | Gamma | ORBIT |
| Mod. | Base case | £149.64 | £14.21 | 110.89 | 0.74 | Gamma | ORBIT |
| | Scenario | £166.91 | £16.69 | | | Gamma | ORBIT + assumption |
| Severe | Base case | £218.28 | £21.40 | 104.04 | 0.48 | Gamma | ORBIT |
| | Scenario | £235.06 | £23.51 | | | Gamma | ORBIT + assumption |
| Very severe | Base case | £218.28 | £21.40 | 104.04 | 0.48 | Gamma | ORBIT |
| | Scenario | £235.06 | £23.51 | | | Gamma | ORBIT + assumption |
| No tics | | £0 | N/A | N/A | N/A | Fixed | Assumption |

**Abbreviations:** SE, Standard error; ERP, Exposure and response prevention
* SE was calculated as 10% of the mean

**Model parameters - health state utility values (HSUVs)**

HSUVs were obtained from the ORBIT study. In the ORBIT study, utilities were calculated from responses to the CHU9D.[53, 54] Responses within the trial were provided by a mix of patient (young person) and proxy (assumed parent) reports at baseline and at 3, 6, 12 and 18

months follow up. It is unclear whether child self-reports, parent proxy-report or a combination of both were used to derive health state utility values for application in the model. Responses to the CHU-9D were converted to utilities using a preference-based algorithm.[55] As with costs above, mild and very mild states incurred the same utility as did severe / very severe states. For the scenario analysis that includes the semi-absorbing tics free state, utility is assumed to be equal to the very mild / mild health state, acknowledging that people with tics and TS often have multiple co-morbidities and it would likely be inappropriate to assign UK general population norms, despite the absence of tics.

Table 21 summarises the HSUVs obtained from the ORBIT trial data and applied in the model. All utilities are incorporated using beta distributions. When applied to health states, QALY payoffs were halved to accommodate the 6-month cycle duration. The utility of the death state is set to zero. All utility inputs to the model are age and sex adjusted, allowing for reduced HSUVs in all health states as the cohort ages through the model. Adjustment multipliers were calculated as general population EQ-5D based utility at each stage / general population utility at the start age of the model cohort. At any given time, the UK general population norm is calculated using the method described by Ara and Brazier (2010).[56]

**Table 21 Utilities associated with each health state**

| Parameters | Mean | SE | alpha | Beta | Dist. | Notes / source |
|---|---|---|---|---|---|---|
| Mild | 0.867 | 0.006 | 2776.21 | 425.88 | Beta | ORBIT |
| Moderate | 0.839 | 0.004 | 7082.37 | 1359.07 | Beta | ORBIT |
| Severe | 0.814 | 0.005 | 4928.90 | 1126.26 | Beta | ORBIT |
| No tics | 0.867 | 0.006 | 2776.21 | 425.88 | Fixed | Assumed equal to utility of the mild state. |

SE. standard error is equal to the standard deviation of the distribution.

*Evidence gaps: As demonstrated in the clinical-effectiveness review, the relationship between tic severity and HRQoL is unclear. Changes in the clinical outcome do not necessarily lead to changes in quality of life or health state utility values. This is an important area for future research. Whilst some evidence is available from the ORBIT study for children, there are no studies reporting the relationship between tic severity and EQ-5D in adult patients. The EAG understands the rationale for pooling very mild / mild and very severe / severe states for calculating HSUVs. However, if a true relationship between tic severity and generic HRQoL exists, the approach may underestimate the QALY benefits of effective treatments. It is unclear if the lack of statistical significance of health state in the ORBIT study is due to small*

*sample sizes, or a true lack of effect. Further studies are required to better understand the relationship between tic severity and QALY benefits. The lack of evidence is particularly acute in an adult population.*

**Model analysis**

Results are presented as incremental cost per QALY gained from a UK NHS perspective. Incremental cost-effectiveness ratios (ICERs) were determined for pairwise comparisons of ERP vs. psychoeducation and active Neupulse stimulation vs. waitlist control.
The cost-effectiveness of each intervention versus comparators was evaluated at an indicative threshold value of £20 000 to £30 000 per QALY gained.[57]

The model is constructed to be fully probabilistic. Probabilistic analyses were performed for each modelling scenario, using Monte Carlo simulation with 50,000 iteration runs (the minimum number of runs required to achieve convergence of probabilistic ICERs), to construct the cost-effectiveness acceptability curves (CEACs). This involved varying the inputs by randomly assigning parameter values from predefined uncertainty distributions as described in the model input parameter tables. A probability distribution was assigned to each model input parameter, reflecting the degree of uncertainty due to sampling variation. Gamma distributions were applied to represent uncertainty surrounding cost inputs, beta distributions were used for utility parameters, and Dirichlet distributions[58] were applied for transition probabilities. When standard errors for parameters were unknown, they were assumed to be 10% of the parameter value to define the PSA distributions. The CEACs show the probability of an intervention being cost-effective compared to comparators for a range of cost-effectiveness threshold values. Results are also presented as iterations of simulations for intervention vs. comparator on the cost-effectiveness plane to illustrate the impact of parameter uncertainty on results.

***Scenario analysis***

There are multiple points of residual uncertainty surrounding many of the key assumptions and model inputs, both for the comparison of ORBIT vs. online psychoeducation and Neupulse vs. waitlist control. This renders it difficult for the EAG to define a clear set of base case assumptions. However, we have selected a set of assumptions that, on balance, appear plausible as a starting point and conduct extensive scenario analyses around these. Table 22 summarises some of the key assumptions, residual uncertainties and EAG scenarios conducted to illustrate that uncertainty.

**Model validation and face validity checks**

One health economist built and parameterised the economic model. Model formulae and parameter inputs were cross checked against source by a second health economist, who also conducted a range of face validity checks, changing one model parameter at a time and re-running results to assess consistency. Adaptations were made where issues were identified. The EAG were unable to identify any longer-term data against which the model outputs could be externally validated. The model outputs were instead presented and discussed amongst the team and clinical experts did not identify any issues of concern regarding the plausibility of the outputs. However, they did flag that the highly uncertain evidence base meant that caution should be exercised when interpreting the results of a lifetime horizon model, given the lack of longer term follow up beyond 18 months for ORBIT and lack of published transition probability data for Neupulse.

The EAG has undertaken a range of further verification tests, based on an adaption of those proposed by Tappenden et al.[59] The results of these verification checks are provided in Table 23 below, applied to the EAG's preferred base case analysis. No further issues were identified with the final version of the EAG's model.

**Table 22 Base case assumptions, residual uncertainties and EAG scenario analyses**

| Assumption / parameter | Base case | Residual uncertainty | Scenario analyses completed |
|---|---|---|---|
| All parameter inputs | Sampled from probabilistic distributions | Parameters are highly uncertain, in particular transition probabilities | Parameter uncertainty incorporated through probabilistic analyses. |
| Potential for some people to become permanently 'tics free' longer term | Assumed not possible | Some people may 'grow out' of tics longer term, into adulthood, but it is unclear to what extent this can be assumed for the modelled population. Duration to achieve 'tics free' and potential to do so are key residual uncertainties. | Inclusion of a tics free semi-absorbing health state in the model. |
| Long term transition probability extrapolation assumptions | Last observed transition carried forward for the full model time horizon | Long-term transition probabilities beyond observed periods are unknown and it is unknown what level of resource use would be required to maintain effectiveness. | Cohort fixed in last observed health state; intervention arm transferred to control group transitions beyond observed time period; shorter time horizons of 2,5 and 10 years explored. |
| ERP and psychoeducation intervention costs | BiP platform costs included in both study arms; ongoing platform usage would be required to maintain effectiveness longer term | It is unclear to what extent the costs incurred in the trial for the BiP platform would be incurred in the psychoeducation arm in routine clinical practice, or whether longer term resource use would be required to maintain effectiveness. | BiP platform costs removed from psychoeducation arm, costs of ongoing use of the platform removed, platform throughput varied between 100 and 1000 for 'per person' cost calculations. |

| Assumption / parameter | Base case | Residual uncertainty | Scenario analyses completed |
|---|---|---|---|
| | | | |
| Health state costs | Obtained from the ORBIT study, includes only the costs of using specialist tic services | The ORBIT economic model may not have captured all the variability in health state costs due to exclusion of other services (e.g. medication costs) | Additional medication costs included as a scenario analysis in the moderate and severe health states based on clinical expert advice. |

**Table 23 'Black box' verification checks conducted on the EAG base case model**

| Model component | Model test | Unequivocal criterion for verification | Issues |
|---|---|---|---|
| **Model component** | **Model test** | **Unequivocal criterion for verification** | **Issues** |
| Clinical trajectory | Apply online psychoeducation probabilities to the ERP, equalize starting proportions and apply equal QALY gains from the trial to both arms. | All treatments produce equal estimates of mean total QALYs. | None |
| | Sum health state occupancy at any model timepoint | Total probability equals 1.0 | None |
| Long-term extrapolation | Fix cohort in last observed state from the ORBIT trial | ICER reduced, NMB increased | None |
| Discounting | Set discount rate to 0 | Costs and QALYs in both arms increase. | None |
| QALY estimation | Set discount rate to a large number | Costs and QALYs in both arms tend to 0. | None |
| QALY estimation<br>Cost estimation | Set all HSUVs for living states = 1; set probability mortality to 0; remove QALY discounting; Set trial QALYs = 1.5 yrs. | QALY gains equal to modelled time horizon + 1.5 years | None |
| | Set intervention costs to 0 | ICER is reduced, NMB increased, probability of cost-effectiveness increased. | None |
| Input parameters | Increase intervention cost | ICER is increased, NMB reduced, probability of cost-effectiveness reduced. | None |
| Input parameters<br>General | Produce n samples of model parameter m | Range of sampled parameter values does not violate characteristics of statistical distribution. | None |
| | Set all treatment-specific parameters equal for all treatment groups (implemented by removing all re-definitions from the ERP node in the model). | Costs and QALYs equal for all treatments | None |

**Key:** ICER incremental cost-effectiveness ratio, NMB, net monetary benefit, QALY quality-adjusted life-year
* Note this assumes that the parameter is part of the total cost function and/or total QALY function

**Results - ORBIT**

***Markov cohort traces***

Figures 10 and 11 illustrate the base case Markov cohort traces for ORBIT and online psychoeducation respectively over a lifetime horizon. The cohort traces are very similar, particularly after the first few model cycles. This is due to differences up to 18 months being quite quickly offset by slightly favourable, but highly uncertain transition probabilities for online psychoeducation.

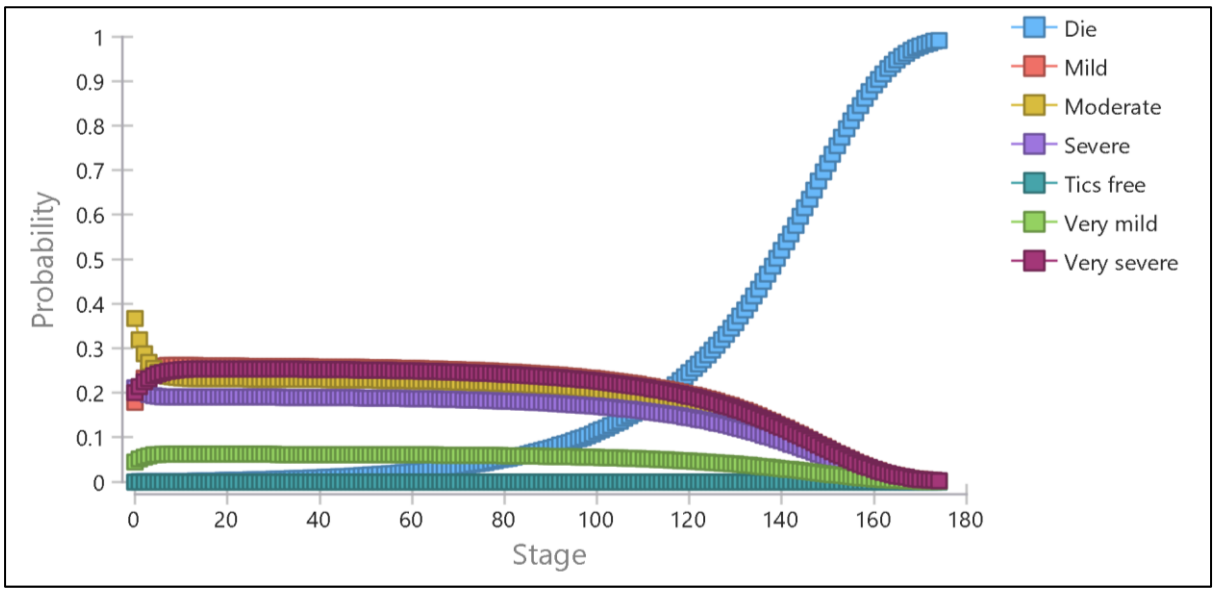


**Figure 10 Markov cohort trace – online psychoeducation**

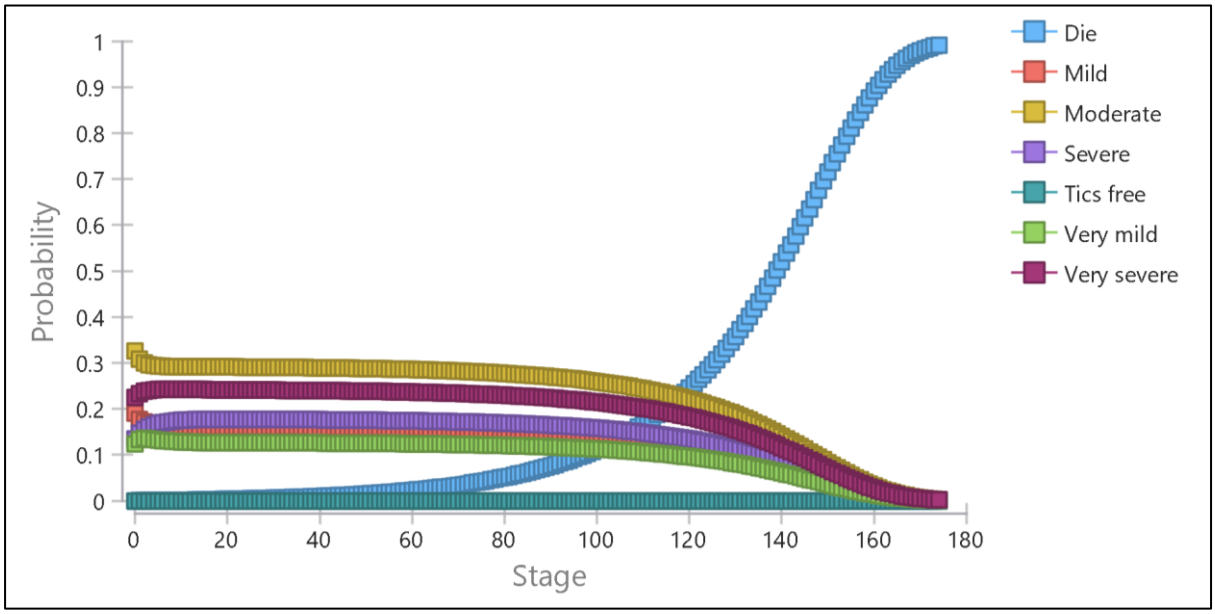


**Figure 11 Markov cohort trace – ORBIT**

***Base-case analysis***

It was not possible to determine a definitive base case set of assumptions. However, a set of assumptions, as outlined in Table 22 are used as a starting point for exploring uncertainty. Probabilistic and deterministic ICERs are reported in Table 24. The deterministic analysis suggests a low ICER of £9,289 for ORBIT compared to online psychoeducation, whereas the probabilistic ICER shows ORBIT to be, on average, more costly with minimal differences in effectiveness (i.e. dominated by online psychoeducation). Whilst these results may appear significantly different to each other, they should be interpreted in the context of the uncertainty surrounding the results output. The magnitude of QALY gains and losses are small in the context of a lifetime horizon, driven by broadly similar transition probabilities for both arms of the model, slightly favouring online psychoeducation, offsetting early QALY gains observed in the trial.

The results should be interpreted considering the uncertainty surrounding the model outputs. Observation of the spread of iterations from the 50,000 iterations from the probabilistic analysis on the cost-effectiveness plane (Figure 12) indicate substantial uncertainty. An approximately equal proportion of iterations lie above and below the £20,000 per QALY threshold line, indicating that neither strategy is clearly optimal under base case assumptions. Furthermore, many of the simulated cost and effect pairs lie in the northwest quadrant of the plane, indicating that we cannot rule out ERP being more costly and less effective over a lifetime horizon. CEACs, provided in Figure 13 also illustrate that the uncertainty persists across all threshold values of willingness to pay for a QALY gain.

**Table 24 Base-case incremental analysis (ORBIT vs. online psychoeducation)**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) |
|---|---|---|---|---|---|
| **Deterministic ICER** | | | | | |
| Psychoeducation | £12,755 | 20.916 | - | - | - |
| ERP | £12,974 | 20.939 | £218 | 0.024 | £9,289 |
| **Probabilistic ICER** | | | | | |
| Psychoeducation | £12,731 | 20.928 | - | - | - |
| ERP | £13,085 | 20.921 | £354 | -0.007 | Dominated |

**Abbreviations:** QALY, quality adjusted life years; ICER, incremental cost-effectiveness ratio; ERP, Exposure, and response prevention

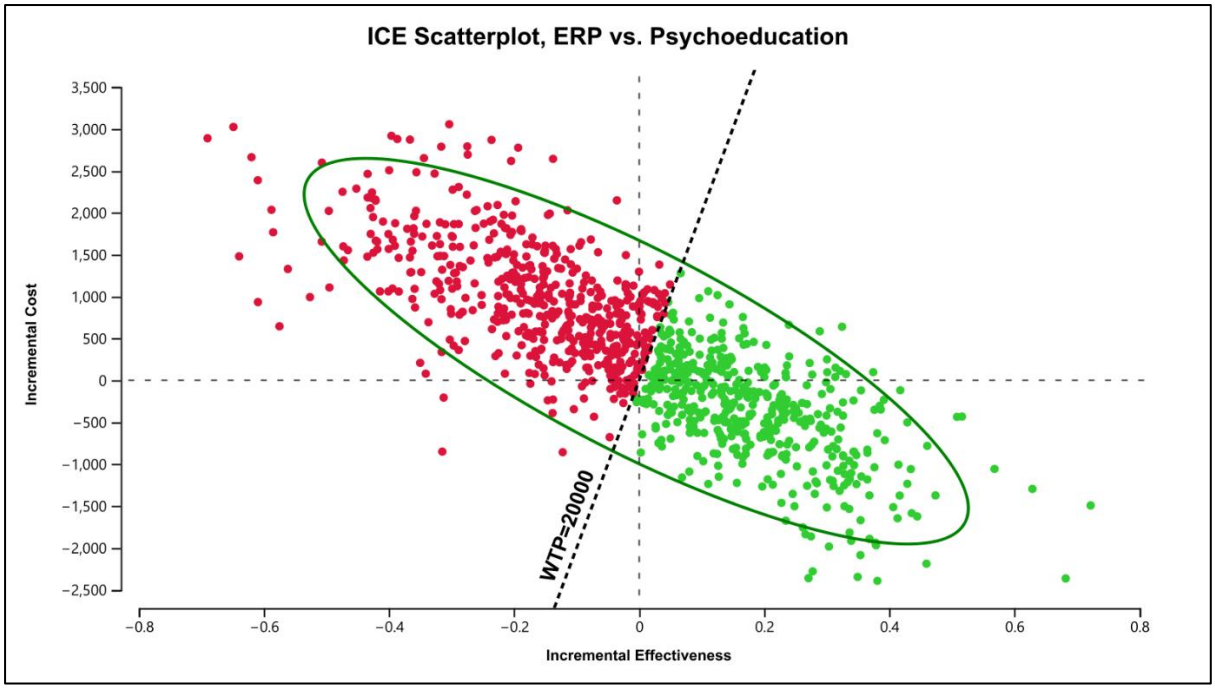


**Figure 12 Base case incremental scatter plot of simulations on the cost-effectiveness plane for ORBIT vs. online psychoeducation**

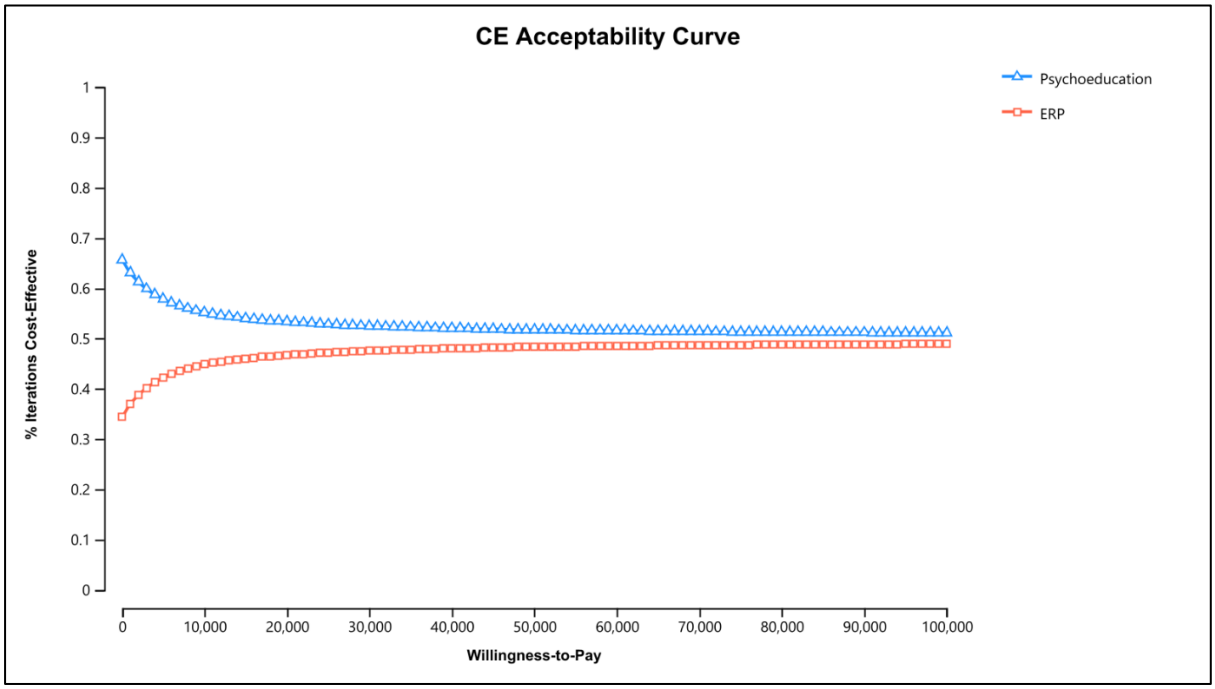


**Figure 13 Base case cost-effectiveness acceptability curves for ORBIT and online psychoeducation.**

***Scenario analysis***

The results of a range of scenario analyses described throughout the report and summarised in Table 22 are provided to further explore uncertainty surrounding key modelling assumptions, including intervention costing, long-term extrapolation of transition probabilities and the potential for inclusion of a tics free semi-absorbing state in the model. Results of the scenario analyses are reported in Table 25. All analyses are probabilistic, based on 50,000 iterations, and probabilities of cost-effectiveness at a £20,000 and £30,000 threshold value of willingness to pay for a QALY gain are reported for completeness, and to illustrate the residual decision uncertainty. Accompanying deterministic results are provided in Appendix 4. In general results were most sensitive to assumptions about the costs of psychoeducation, including whether the variable costs of the platform are included. When combined with uncertainty around the most appropriate extrapolation assumptions, uncertainty increased further. It should be noted that the analysis, re-setting transition probabilities to the psychoeducation arm might be anticipated to increase the ICER substantially if ERP was clearly more effective than psychoeducation. However, this is not the case, demonstrating the impact of the very similar transition matrices between arms when extrapolated over a long-term time horizon.

The probability of ORBIT being cost-effective at a willingness to pay threshold of £20,000 per QALY gained varies between 45% up to 90% in a highly optimistic scenario where it is assumed that the cohort remain in their last observed health state at the end of the trial follow-up period.

**Table 25 Scenario analyses for comparison of ORBIT vs. online psychoeducation (probabilistic)**

| S. No | Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) | Probability cost-effective @ various values of lambda | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | £20,000 | £30,000 |
| **0** | **Base case** | | | | | | | |
| | Psychoeducation | £12,731 | 20.928 | - | - | - | 0.53 | 0.52 |
| | ERP | £13,085 | 20.921 | £354 | -0.007 | Dominated | 0.47 | 0.48 |
| **1** | **Time horizon = 10 years from end of trial follow-up (18 months + 10 years)** | | | | | | | |
| | Psychoeducation | £5,123 | 7.741 | - | - | - | 0.45 | 0.42 |
| | ERP | £5,417 | 7.763 | £294 | 0.023 | £12,867 | 0.55 | 0.58 |
| **2** | **Times horizon = 5 years from end of trial follow-up (18 months + 5 years)** | | | | | | | |
| | Psychoeducation | £3,422 | 4.593 | - | - | - | 0.37 | 0.32 |
| | ERP | £3,707 | 4.622 | £285 | 0.029 | £9,936 | 0.63 | 0.68 |
| **3** | **Time horizon = 2 years from end of trial follow-up (18 months + 2 years)** | | | | | | | |
| | Psychoeducation | £2,253 | 2.413 | - | - | - | 0.32 | 0.25 |
| | ERP | £2,541 | 2.443 | £289 | 0.030 | £9,611 | 0.68 | 0.75 |
| **4** | **Include transitions into the absorbing 'tics free' health state, set utility tics free = mild** | | | | | | | |
| | Psychoeducation | £5,947 | 21.311 | - | - | - | 0.50 | 0.48 |
| | ERP | £6,254 | 21.324 | £306 | 0.013 | £22,979 | 0.50 | 0.52 |
| **5** | **Include only variable cost of therapist support for psychoeducation** | | | | | | | |

| S. No | Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) | Probability cost-effective @ various values of lambda | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | £20,000 | £30,000 |
| | Psychoeducation | £12,495 | 20.928 | - | - | | 0.55 | 0.54 |
| | ERP | £13,088 | 20.921 | £593 | -0.007 | Dominated | 0.45 | 0.46 |
| **6** | **Apply approach from ORBIT study (include only variable platform costs and therapist support for psychoeducation; remove all ongoing costs)** | | | | | | | |
| | Psychoeducation | £12,489 | 20.928 | - | - | | 0.54 | 0.53 |
| | ERP | £12,936 | 20.922 | £447 | -0.006 | Dominated | 0.46 | 0.47 |
| **7** | **Only include variable therapist support costs, include ongoing costs + platform throughput (n=100)** | | | | | | | |
| | Psychoeducation | £12,615 | 20.927 | - | - | - | 0.55 | 0.53 |
| | ERP | £13,145 | 20.920 | £530 | -0.007 | Dominated | 0.45 | 0.47 |
| **8** | **Only include variable therapist support costs, include ongoing costs + platform throughput (n=1000)** | | | | | | | |
| | Psychoeducation | £12,603 | 20.928 | - | - | - | 0.54 | 0.53 |
| | ERP | £13,054 | 20.920 | £451 | -0.008 | Dominated | 0.46 | 0.47 |
| **9** | **Remove ongoing costs from both arms** | | | | | | | |
| | Psychoeducation | £12,619 | 20.928 | - | - | - | 0.53 | 0.52 |
| | ERP | £12,946 | 20.922 | £327 | -0.006 | Dominated | 0.47 | 0.48 |
| **10** | **Remove long-term transition probabilities (retain in state beyond 18 months), assumes 18-month benefit retained indefinitely** | | | | | | | |
| | Psychoeducation | £12,647 | 20.871 | - | - | - | 0.10 | 0.11 |

| S. No | Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) | Probability cost-effective @ various values of lambda | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | £20,000 | £30,000 |
| | ERP | £12,723 | 20.989 | £76 | 0.119 | £642 | 0.90 | 0.89 |
| **11** | **ERP transition probabilities revert to online psychoeducation arm after 18 months** | | | | | | | |
| | Psychoeducation | £12,730 | 20.928 | - | - | - | 0.29 | 0.22 |
| | ERP | £13,010 | 20.962 | £281 | 0.033 | £8,419 | 0.71 | 0.78 |
| **12** | **Apply additional medication costs to moderate and severe health states** | | | | | | | |
| | Psychoeducation | £13,416 | 20.929 | - | - | - | 0.54 | 0.53 |
| | ERP | £13,830 | 20.921 | £415 | -0.008 | Dominated | 0.46 | 0.47 |

**Abbreviations:** QALY, quality adjusted life years; ICER, incremental cost-effectiveness ratio; lambda, Society's threshold value of willingness to pay for a QALY gained; ERP, Exposure and response prevention

**Results - Neupulse**

***Markov cohort traces***

Figures 14 and 15 show the modelled Markov cohort traces for Neupulse and waiting list control (assumed standard of care) respectively.

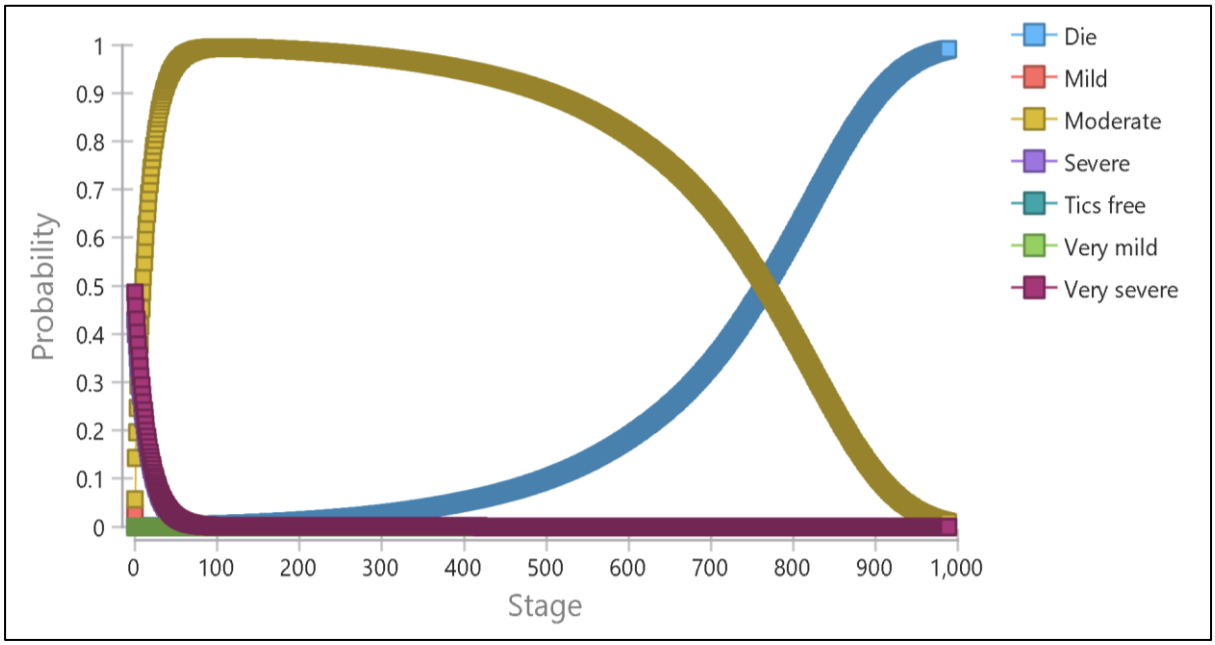


**Figure 14 Base case Markov cohort traces for wait list control**

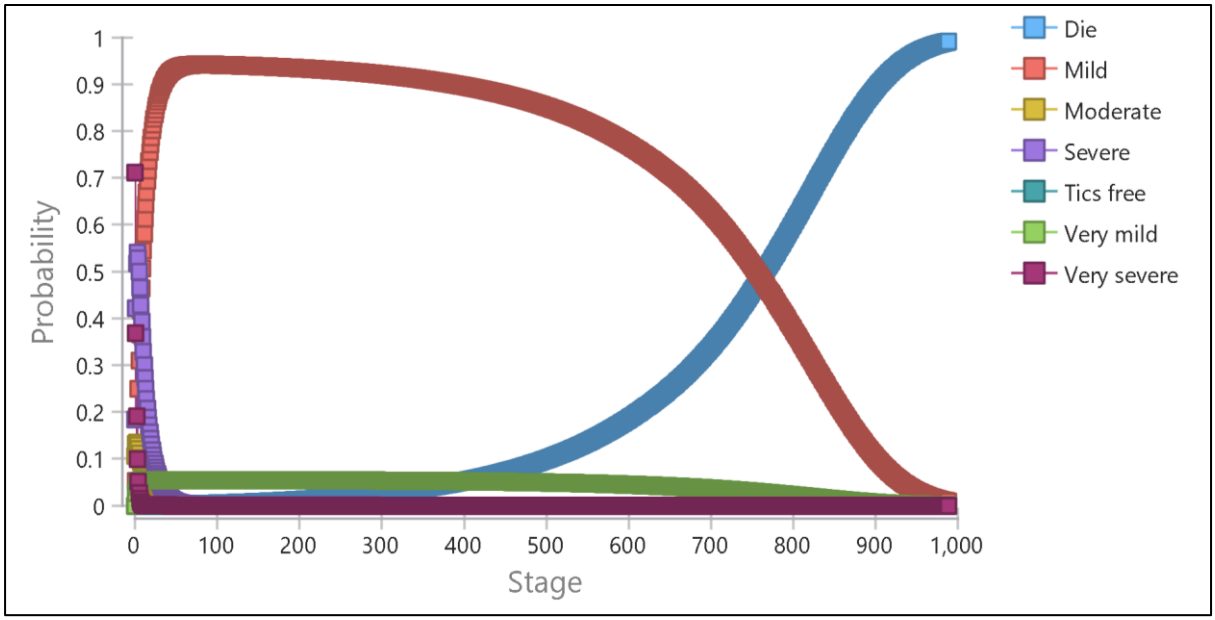


**Figure 15 Base case Markov cohort traces for Neupulse**

The Markov cohort traces show a clear difference between the Neupulse arm, with most of the cohort in the mild health state over time, compared to the waiting list control arm, with

the majority in the moderate health state. These cohort traces reflect the optimistic transition probabilities provided by the company to the EAG. However, it is crucial to note that these are based on one set of transitions, between baseline and 4-weeks only, and are based on very small samples. It is therefore likely that the relative effectiveness of the intervention is overestimated in the longer term as it is highly unlikely that the level of effectiveness seen up to 4-weeks would be maintained over a full lifetime horizon.

***Basecase analysis***

Given the lack of available data to populate the Neupulse model, it is not reasonable to derive a definitive base case analysis. Instead, the potential uncertainty surrounding results should be interpreted across the range of scenario analyses presented. As a starting point, the scenarios from Table 22 are applied to the Neupulse comparison and the deterministic and probabilistic ICERs are presented in Table 26. Neupulse is almost [redacted] as costly as the waiting list control at the prices provided by the company. The additional costs are driven by [redacted] device replacement and the [redacted], which would be the minimum costs required to allow extrapolation of highly optimistic 4-weekly transition probabilities over a lifetime horizon. This scenario likely represents the maximum feasible QALY gain that could be achieved if an intervention could almost entirely resolve all tics to the 'mild tics' health state. Whether this is achievable longer-term is unclear. Results of the probabilistic analyses are illustrated on the cost-effectiveness plane and using CEACs in figures 16 and 17 respectively.

**Table 26 Base-case incremental analysis (Neupulse vs. Waiting list control)**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) |
|---|---|---|---|---|---|
| **Deterministic ICER** | | | | | |
| Waiting list control | £7,693 | 19.138 | - | - | - |
| Neupulse | [redacted] | 19.765 | [redacted] | 0.627 | [redacted] |
| **Probabilistic ICER** | | | | | |
| Waiting list control | £7,796 | 19.118 | - | - | - |
| Neupulse | [redacted] | 19.690 | [redacted] | 0.572 | [redacted] |

**Abbreviations:** QALY, quality adjusted life years; ICER, incremental cost-effectiveness ratio; ERP, Exposure and response prevention

**Figure 16 Incremental scatter plot of simulations on the cost-effectiveness plane for Neupulse vs. wait list control**

**Figure 17 Cost-effectiveness acceptability curves for Neupulse and wait list control**

***Scenario analysis***

The results of scenario analyses conducted to explore the sensitivity of the base case results to a range of modelling assumptions are described in Table 27. All analyses are probabilistic with the probability of cost-effectiveness indicated. Results were most sensitive to

assumptions about the long-term extrapolation from 4-weeks onwards, clearly demonstrating the need for future research around long-term effectiveness. Different assumptions cause wide variation in the ICER between just over £10,000 per QALY gained in an optimistic scenario analysis that extrapolates 4-weekly transitions for a lifetime (probability of cost-effective = 87%) to over £300,000 per QALY in the less optimistic scenario analysis (probability cost-effective = 0%) where transitions are crossed over to the waitlist control group after the observed 4-week period. Deterministic analyses are provided in Appendix 4.

Given that the confidential nature of initial and ongoing Neupulse intervention costs, two-way scenario analyses are conducted to illustrate the impact of varying intervention and subscription costs on results. These scenarios are applied to two alternative assumptions about long-term transition probabilities (4-weekly transitions are carried forward, and the cohort fixed in state after 4 weeks, assuming maximum effectiveness achieved at 4 weeks). Analyses are based on NMBs with a WTP = £20,000 per QALY. Results are reported in Figures 18 and Figure 19. Results of these analyses further emphasise the substantial residual uncertainty regarding intervention costs and long-term extrapolation assumptions.

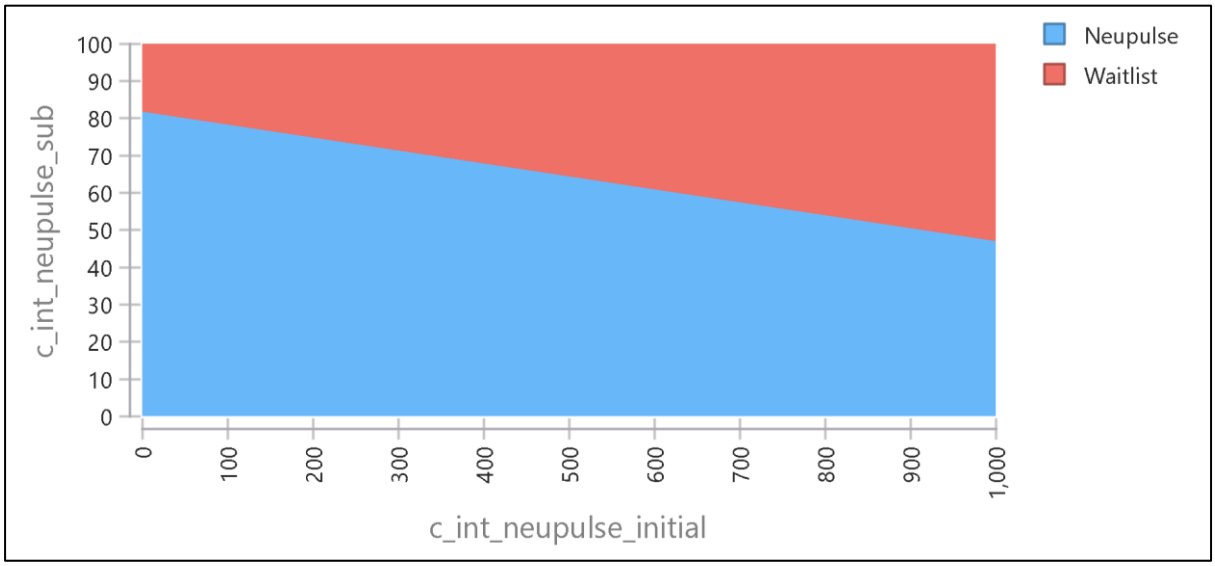


**Figure 18 Two-way scenario analysis of initial and subscription costs for Neupulse (assumes long-term transition probabilities extrapolated)**

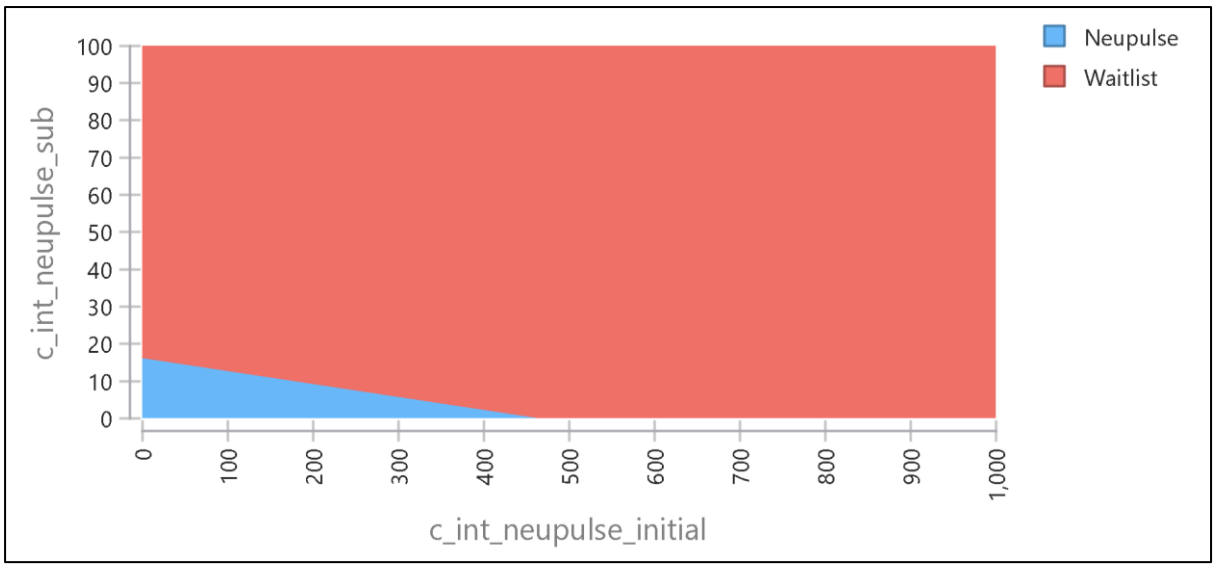


**Figure 19 Two-way scenario analysis of initial and subscription costs for Neupulse (assumes cohort held in last observed state)**

**Table 27 Scenario analyses for comparison of Neupulse vs. wait list control (probabilistic)**

| S. No | Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) | Probability cost-effective @ various values of lambda | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | £20,000 | £30,000 |
| | **Base case** | | | | | | | |
| **0** | Wait list control | £7,796 | 19.118 | - | - | - | 0.14 | 0.07 |
| | Neupulse | [redacted] | 19.690 | [redacted] | 0.572 | [redacted] | 0.88 | 0.93 |
| | **Time horizon = 10 years** | | | | | | | |
| **1** | Wait list control | £2,830 | 6.924 | | | | 0.24 | 0.16 |
| | Neupulse | [redacted] | 7.110 | [redacted] | 0.186 | [redacted] | 0.76 | 0.84 |
| | **Time horizon = 5 years** | | | | | | | |
| **2** | Wait list control | £1,600 | 3.742 | | | | 0.33 | 0.23 |
| | Neupulse | [redacted] | 3.835 | [redacted] | 0.092 | [redacted] | 0.67 | 0.77 |
| | **Time horizon = 2years** | | | | | | | |
| **3** | Wait list control | £710 | 1.535 | | | | 0.56 | 0.39 |
| | Neupulse | [redacted] | 1.566 | [redacted] | 0.031 | [redacted] | 0.44 | 0.61 |
| | **Include transitions into the absorbing 'tics free' health state, set utility tics free = mild** | | | | | | | |
| **4** | Wait list control | £3,330 | 19.475 | - | - | - | 0.17 | 0.10 |
| | Neupulse | [redacted] | 19.721 | [redacted] | 0.247 | [redacted] | 0.83 | 0.90 |

| S. No | Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) | Probability cost-effective @ various values of lambda | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | £20,000 | £30,000 |
| 5 | **Long-term transition probabilities: set equal to zero, assumes no further improvement of regression of tics and TS after 4 weeks** | | | | | | | |
| | Wait list control | £10,703 | 18.659 | - | - | - | 0.99 | 0.91 |
| | Neupulse | [redacted] | 18.763 | [redacted] | 0.104 | [redacted] | 0.01 | 0.09 |
| 6 | **Long-term transition probabilities: assume that Neupulse cohort reverts to 'no treatment' transition matrix after 4 weeks** | | | | | | | |
| | Wait list control | £7,802 | 19.119 | - | - | - | 1 | 1 |
| | Neupulse | [redacted] | 19.141 | [redacted] | 0.022 | [redacted] | 0 | 0 |
| 7 | **Apply additional medication costs to moderate and severe health states** | | | | | | | |
| | Wait list control | £8,675 | 19.119 | - | - | - | 0.11 | 0.93 |
| | Neupulse | [redacted] | 19.690 | [redacted] | 0.572 | [redacted] | 0.89 | 0.07 |

**Abbreviations:** QALY, quality adjusted life years; ICER, incremental cost-effectiveness ratio; lambda, Society's threshold value of willingness to pay for a QALY gained.

## Interpretation of the evidence and conclusions

### Statement of principal findings

Following comprehensive searches of the current literature, two studies comparing ORBIT with psychoeducation (one each in the UK[33] and Sweden[37]) and one UK study comparing active stimulation with sham stimulation[35] were included in the review of clinical effectiveness. All were assessed as being at low risk of bias. The majority of intermediate, clinical and patient-reported outcomes specified in the scope were reported across the three studies, but the actual measures utilised and time points they were administered were not consistent across studies. In general, tic severity scores measured using the YGTSS-TTSS (primary outcome) were lower in the respective intervention groups at follow-up periods ranging from four weeks (Neupulse)[35] to 12 months (the two ORBIT studies).[33, 37] However, no improvements were observed in all three studies concerning the YGTSS-Impairment score. Responses to secondary outcome measures were mixed and participants did not consistently show a better response to the intervention compared with the control at all assessed time points and across studies. In general, level of engagement, adherence to treatment and dropouts were similar between intervention groups.

Economic modelling shows that there remains substantial residual uncertainty in the assessment of cost-effectiveness for both interventions. Key areas of remaining uncertainty include:

- non-publicly available Neupulse pricing information,
- short follow-up of only 4-weeks for Neupulse,
- Unclear long-term intervention costs that would be required to deliver trial observed benefits,
- Uncertainty about the most appropriate link between tic severity score and health state costs and utilities, in particular whether small improvements in YGTSS scores have a direct impact on generic quality of life measures such as EQ-5D or CHU-9D,
- A lack of information about long-term effectiveness beyond the trial follow up periods to inform economic modelling

### Strengths and limitations of the assessment and uncertainties

This assessment was conducted using thorough and robust methods. The main limitation of the systematic review of clinical effectiveness was the paucity of

evidence for the technologies of interest. The limited amount of evidence and inconsistencies in the outcomes measured and the timing of these measurements also hampered efforts to conduct further meaningful analyses.

The identified studies did not involve a comparison with face-to-face behavioural therapy, which is the current standard of care. Therefore, for the ORBIT studies, it was not possible to separate the effects of online delivery from those of ERP. Moreover, both ORBIT studies did not include a non-active control treatment (e.g. waitlist) to evaluate the natural course of the disease over time, especially in young children.

While a reduction of tic severity measured by the YGTSS-TTSS score was greater among participants receiving the intervention (digitally-enabled ERP in the ORBIT studies and home-administered median nerve stimulation in the Neupulse study) the fact that there were no improvements in the YGTSS-Impairment score casts some doubt on whether a reduction in tic severity translates into an improvement in daily life including self-esteem, social interactions and school/work performance. Similarly, the inconsistent improvements in quality-of-life measures (i.e. C&A-GTS-QOL) over follow-up times and across studies, reinforce this doubt.

It is also unclear why only the YGTSS-TTSS score was selected as the primary outcome in the included studies but not the YGTSS-Impairment score.

Both ORBIT studies included participants with moderate to severe tic disorders, who had a low rate of common comorbidities and modest use of medications for tics. Therefore, the reported findings cannot be generalisable to more severe tic disorder populations. Similarly, most participants in at least one of the ORBIT studies (the UK study) were White, which limits the generalisation of findings to other ethnic groups.

The longest follow-up period in the UK ORBIT study and the Swedish ORBIT study was 18 and 12 months, respectively. The current data for Neupulse, which has been designed to control tic symptoms on demand, refer to stimulation delivered for a maximum of 4 weeks. There are no data on longer durations of stimulation or longer-term outcomes to inform economic modelling.

The assessment of cost-effectiveness relied on several major, but highly uncertain assumptions about longer term intervention costs that might be required to maintain

the intervention's effectiveness as well as the most appropriate long-term extrapolation assumptions. Scenario and probabilistic sensitivity analyses show that there is substantial residual uncertainty, making it difficult to define the most plausible ICERs for either comparison.

**Key areas for future research**

- As the included studies are the first published adequately powered randomised studies to assess the technologies under investigation, future replication is needed to confirm the observed results.
- Future studies of longer duration should compare digitally enabled therapy for tics versus face-to-face behavioural therapy and should also consider including a non-active intervention (e.g., waitlist) to monitor the natural course of the disease over time.
- In addition to tic severity, future studies should measure the impact of digitally enabled therapy on participants' daily lives as their primary outcome.
- To assess differences in treatment response among participants, future studies should plan appropriate subgroup analyses according to the participants' sex distribution (males versus females) and common comorbidities.
- Future studies should include economic evaluations and should consider collection of longitudinal data to improve long-term modelling of treatment effectiveness with a focus on determining the impact of changes in clinical outcomes on quality of life and costs.

## References


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# Appendices

## Appendix 1 Literature search strategies

### *Clinical*

**Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to February 05, 2024>**

1 Tics/ or exp Tic Disorders/ or (tic or tics or Tourette?).tw,kw. 14781

2 exp Behavior Therapy/ or psychotherapy/ 145391

3 (((psycho* or behavio* or cognitive) adj5 (therap* or intervention? or treatment or program* or training)) or psychotherapy).tw,kw. 259594

4 ("Habit Reversal Training" or HRT or "Comprehensive Behavio?ral Intervention for Tics" or CBIT or "Exposure and response prevention" or ERP).tw,kw. 31475

5 2 or 3 or 4 367217

6 Internet/ or Online Systems/ or Internet-Based Intervention/ or Mobile Applications/ or Cell Phone/ or Smartphone/ or telemedicine/ or videoconferencing/ 149679

7 (digital or remote or online or web or internet or technology or app? or computer or mobile or smart phone or smartphone or virtual or tele* or video*).tw,kw. 1860466

8 Wearable Electronic Devices/ or ((wearable adj7 (technolog* or device?)) or wearables).tw,kw. 19151

9 (ORBIT or Mindtech or Neupulse or Neurotherapeutics).af. 55382

10 (6 or 7 or 8 or 9) not "Telephone Interview for Cognitive Status".tw. 1954578

11 1 and 5 and 10 121

12 from 11 keep 1-121 121

**Embase <1974 to 2024 Week 05>**

1 exp Tic/ or (tic or tics or Tourette?).tw,kw. 24974

2 exp Behavior Therapy/ or exp cognitive therapy/ or psychotherapy/ 195463

3 (((psycho* or behavio* or cognitive) adj5 (therap* or intervention? or treatment or program* or training)) or psychotherapy).tw,kw. 346715

4 ("Habit Reversal Training" or HRT or "Comprehensive Behavio?ral Intervention for Tics" or CBIT or "Exposure and response prevention" or ERP).tw,kw. 42982

5 2 or 3 or 4 472798

6 Internet/ or Online Systems/ or web-based intervention/ or mobile application/ or mobile phone/ or Smartphone/ or telemedicine/ or telepsychology/ or teletherapy/ or video consultation/ or videoconferencing/ 258798

7 (digital or remote or online or web or internet or technology or app? or computer or mobile or smart phone or smartphone or virtual or tele* or video*).tw,kw. 2390370

8 Wearable computer/ or ((wearable adj7 (technolog* or device?)) or wearables).tw,kw. 16895

9 (ORBIT or Mindtech or Neupulse or Neurotherapeutics).af. 71797

10 (6 or 7 or 8 or 9) not "Telephone Interview for Cognitive Status".tw. 2526602

11 1 and 5 and 10 239

12 conference abstract.pt. 5038585

13 11 not 12 186

**APA PsycInfo <1967 to January Week 5 2024>**

1 Tics/ or exp Tic Disorders/ or (tic or tics or Tourette?).tw,id. 7117

2 exp Behavior Therapy/ or psychotherapy/ 165748

3 (((psycho* or behavio* or cognitive) adj5 (therap* or intervention? or treatment or program* or training)) or psychotherapy).tw,id. 350593

4 ("Habit Reversal Training" or HRT or "Comprehensive Behavio?ral Intervention for Tics" or CBIT or "Exposure and response prevention" or ERP).tw,id. 17786

5 2 or 3 or 4 420407

6 Internet/ or Digital Interventions/ or Mobile Phones/ or Smartphones/ or Mobile Applications/ or exp Telemedicine/ 54857

7 (digital or remote or online or web or internet or technology or app? or computer or mobile or smart phone or smartphone or virtual or tele* or video*).tw,id. 522816

8 Wearable Devices/ or ((wearable adj7 (technolog* or device?)) or wearables).tw,id. 1909

9 (ORBIT or Mindtech or Neupulse or Neurotherapeutics).af. 21883

10 (6 or 7 or 8 or 9) not "Telephone Interview for Cognitive Status".tw. 544776

11 1 and 5 and 10 145

**CINAHL**

S1 (MH "Tic") 862

S2 TX tic or tics or Tourette? 586

S3 S1 OR S2 1,176

S4 (MH "Behavior Therapy+") OR (MH "Psychotherapy") 64,275

S5 TX ( (psycho* OR behavio* OR cognitive) N5 (therap* OR intervention? OR treatment OR program* OR training) ) OR TX psychotherapy 213,705

S6 TX "Habit Reversal Training" OR HRT OR "Comprehensive Behavioral Intervention for Tics" OR CBIT OR "Exposure and response prevention" OR ERP 6,117

S7 S4 OR S5 OR S6 225,804

S8 (MH "Internet") OR (MH "Online Systems") OR (MH "Internet-Based Intervention") OR (MH "Mobile Applications") OR (MH "Cellular Phone") OR (MH "Smartphone") OR (MH "Telemedicine") OR (MH "Videoconferencing") 90,713

S9 TX digital OR remote OR online OR web OR internet OR technology OR app? OR computer OR mobile OR "smart phone" OR smartphone OR virtual OR tele* or video*1,043,445

S10 TX ( wearable N7 (technolog* OR device?) ) OR TX wearables 7,325

S11 TX ORBIT OR Mindtech OR Neupulse OR Neurotherapeutics) 5,416

S12 ( S8 OR S9 OR S10 OR S11 ) NOT TX "Telephone Interview for Cognitive Status" 1,057,789

S13 S3 AND S7 AND S12 29

**Web of Science Core Collection**

1: tic or tics or Tourette$ (Topic) 32284

2: (psycho* or behavio* or cognitive) Near/5 (therap* or intervention$ or treatment or program* or training) (Topic) 220662

3: psychotherapy (Topic) 32198

4: "Habit Reversal Training" or HRT or "Comprehensive Behavioral Intervention for Tics" or CBIT or "Exposure and response prevention" or ERP (Topic) 41037

5: #2 OR #3 OR #4 278222

6: digital or remote or online or web or internet or technology or app$ or computer or mobile or "smart phone" or smartphone or virtual or tele* or video* (Topic) 4119359

7: wearable Near/7 (technolog* or device$) (Topic) 24576

8: wearables (Topic) 3888

9: ORBIT or Mindtech or Neupulse or Neurotherapeutics (Topic) 179034

10: #6 OR #7 OR #8 OR #9 4291494

11: #1 AND #5 AND #10 130

**NIHR**

Search: “tics”, “tic disorders”, Tourette: 2, 0 additional

**SIGN**

Browse list: 0

**NICE**

Search: “tics”, “tic disorders”, Tourette

Suspected neurological conditions: recognition and referral NICE guideline [NG127] (Previously supplied)

**AHRQ Evidence Reports**

Search: “tics”, “tic disorders”, Tourette: 0

**CADTH**

Search: “tics”, “tic disorders”, Tourette

Telehealth Services for the Treatment of Psychiatric Issues: Clinical Effectiveness, Safety, And Guidelines

**HIQA**

Search: “tics”, “tic disorders”, Tourette: 0

**IHTA**

MeSH ‘Tic Disorders’; ‘Tourette Syndrome’, “tics”, “tic disorders”, Tourette: 3, 0 additional

**Royal College of Psychiatrists**

Search: “tics”, “tic disorders”, Tourette: 1, 0 additional

**Royal College of Paediatrics and Child Health**

Search: “tics”, “tic disorders”, Tourette: 0

***Health economics***

**Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to March 04, 2024>**

| | | |
|---|---|---|
| 1 | Tics/ or exp Tic Disorders/ or (tic or tics or Tourette?).tw,kw. | 14848 |
| 2 | exp "costs and cost analysis"/ | 269094 |
| 3 | *economics/ | 10813 |
| 4 | economics, hospital/ | 11281 |
| 5 | exp economics,medical/ | 14425 |
| 6 | economics,pharmaceutical/ | 3126 |
| 7 | exp models, economic/ | 16267 |
| 8 | exp decision theory/ | 13578 |

9 monte carlo method/ 32688

10 markov chains/ 16084

11 exp technology assessment, biomedical/ 12284

12 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimis$)).ab. 198457

13 economics model$.tw. 78

14 (economic$ or pharmacoeconomic$).tw. 386784

15 (price or prices or pricing).tw. 53571

16 budget$.tw. 36953

17 (value adj1 money).tw. 41

18 (expenditure$ not energy).tw. 38373

19 markov$.tw. 32744

20 monte carlo.tw. 60753

21 (decision$ adj2 (tree? or analy$ or model$)).tw. 40544

22 ec.fs. 443096

23 or/2-221170130

24 1 and 23 233

**Embase <1974 to 2024 Week 09>**

1 exp Tic/ or (tic or tics or Tourette?).tw,kw. 25056

2 exp economic evaluation/ 364230

3 exp *economics/ 29531

4 health economics/ 36299

5 exp health care cost/ 349378

6 pharmacoeconomics/ 11677

7 exp decision theory/ 1861

8 Monte Carlo method/ 52760

9 Markov chain/ 11114

10 exp biomedical technology assessment/ 17894

11 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimis$)).ab. 267789

12 economics model$.tw. 147

13 (price or prices or pricing).tw. 73206

14 (value adj2 money).tw. 3091

15 (expenditure$ not energy).tw. 51916

16 markov$.tw. 41120

17 monte carlo.tw. 63148

18 (decision$ adj2 (tree? or analy$ or model$)).tw. 54253

19 or/2-18998976

20 1 and 19 431

21 conference abstract.pt. 5065495

22 20 not 21 332

**APA PsycInfo <1967 to February Week 5 2024>**

1 Tics/ or exp Tic Disorders/ or (tic or tics or Tourette?).tw,id. 7144

2 exp Health Care Costs/ or exp "Costs and Cost Analysis"/ 50267

3 *economics/ or health care economics/ 19726

4 pharmacoeconomics/ 293

5 decision theory/ 1379

6 Markov Chains/ 1960

7 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimis$)).ab. 26687

8 economics model$.tw. 52

9 (economic$ or pharmacoeconomic$).tw. 135615

10 (price or prices or pricing).tw. 21221

11 budget$.tw. 10255

12 (value adj1 money).tw. 47

13 (expenditure$ not energy).tw. 9592

14 markov$.tw. 5346

15 monte carlo.tw. 5643

16 (decision$ adj2 (tree? or analy$ or model$)).tw. 11458

17 or/2-16237133

18 1 and 17 103

**CRD Databases (NHS EED, DARE, HTA)**

Tics (MeSH): 2 / 0

Tic disorders (MeSH): 19 / 1

Title: Tic* or Tourette*: 61 / 1

**Proquest EconLit**

noft(tic OR tics OR tourette*)

**CEA**

Keyword: Tourette or tic or tics

Disease: Mental, Behavioral and Neurodevelopmental disorders/Diseases of the nervous system

**NICE**

Search: “tics”, “tic disorders”, Tourette: 2, 0 additional

**NIHR**

Search: “tics”, “tic disorders”, Tourette: 2, 0 additional

**AHRQ Evidence Reports**

Search: “tics”, “tic disorders”, Tourette: 0

**CADTH**

Search: “tics”, “tic disorders”, Tourette

**HIQA**

Search: “tics”, “tic disorders”, Tourette: 0

**IHTA**

Tics (MeSH): 1

Tic disorders (MeSH): 4

## Appendix 2 Characteristics of included studies

### Table 28 Characteristics of included studies

| Study details | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **First author, yr:** Hollis 2021<br>**Secondary reports:** Hall 2019 RefID 206<br>Hall 2020 RefID 197<br>Hollis 2023 RefID 149<br>Hollis 2023 RefID 582<br>Khan 2020 RefID 201<br>Khan 2021 RefID 193<br>Khan 2022 RefID 17<br>**Language:** English<br>**Publication type:** Full text<br>**Setting:** Home<br>**Study design:** RCT<br>**Intervention device:** ORBIT<br>**Comparator:** Psychoeducation | 1. Aged 9–17 years.<br>2. Suspected or confirmed TS or chronic tic disorder. — Including moderate/ severe tics: Total Tic Severity Score >15 on the YGTSS; TTSS score >10 if motor or vocal tics only.<br>3. Competent to provide written, informed consent (parental consent for child aged <16 years).<br>4. Broadband internet access and regular PC/laptop/Mac user, with mobile phone SMS. | 1. Receipt of/engaged in structured behavioural intervention for tics (eg, HRT/CBIT or ERP) within the last 12 months.<br>2. Change to medication for tics (start or stop) within the previous two months.<br>3. Diagnoses of alcohol/substance dependence, psychosis, suicidality or anorexia nervosa.<br>4. Moderate/severe intellectual disability.<br>5. Immediate risk to self or others.<br>6. Parent or child not able to speak or read/write English. |
| **First author, yr:** Andren 2022<br>**Secondary reports:** Andren 2019<br>Andren 2021 RefID 189, Andren 2024<br>**Language:** English<br>**Publication type:** Full text<br>**Setting:** Home<br>**Study design:** RCT<br>**Intervention device:** ORBIT<br>**Comparator:** Psychoeducation | Eligible participants were 9-to-17-year-old children with a DSM-5 diagnosis of TS or CTD1 who had a YGTSS Total Tic Severity Score (TTSS) >15 (or >10 if only motor or vocal tics had been present during the last week), had at least one parent available to participate in the treatment, and had access to at least one computer and one mobile phone per family. | Participants were excluded if they had received ≥8 sessions of BT for tics with a qualified therapist within the past year, were receiving simultaneous psychological treatment for TS/CTD, had initiated or adjusted any psychotropic medication for TS/CTD within the past 8 weeks, had a diagnosis of organic brain disorder, intellectual disability, autism spectrum disorder, psychosis, bipolar disorder, anorexia nervosa or alcohol/substance dependence, were an immediate risk for themselves or others requiring urgent medical attention (e.g., suicidality or self-injurious tics), were not able to read and |

| Study details | Inclusion criteria | Exclusion criteria |
|---|---|---|
| | | communicate in Swedish or had a close relative already enrolled in the trial. |
| **First author, yr:** Maiquez 2023<br>**Secondary reports:** Maiquez 2020<br>**Language:** English<br>**Publication type:** Full text<br>**Setting:** Home<br>**Study design:** RCT<br>**Intervention device:** Neupulse<br>**Comparators:** Sham stimulation; waitlist (not considered for review of clinical effectiveness) | 1. Ages 12 years upward.<br>2. Confirmed or suspected Tourette syndrome/Chronic tic disorder. With moderate–severe tics, indicated by a total tic score > 15 on the Yale global tic severity scale (YGTSS), or total tic score > 10 if only motor/vocal tics are present.<br>3. No change in medication for tics or tic-related treatment in the last 2 months. Participants were to confirm this during telephone screening.<br>4. Broadband internet access and electronic device for completion of online materials. For a subset of participants, a device with a camera will also be required.<br>5. Ability to travel to the University of Nottingham for one onsite visit.<br>6. Participant is willing and able to give informed consent for participation in the clinical investigation.<br>7. Able (in the Investigator's opinion) and willing to comply with all clinical investigation requirements.<br>8. Resident in the United Kingdom. | 1. Current diagnosis of epilepsy.<br>2. Participant or participant's guardian (if under 16) unable to read/write in English.<br>3. Participants will be excluded from the trial if they find the stimulation too uncomfortable during the in-person baseline assessment visit.<br>4. Individuals with implanted electronic devices (e.g. pacemakers, insulin pump, implantable cardioverter defibrillator, neurostimulators).<br>5. Individuals sharing the household with an individual with implanted electronic devices (e.g. pacemakers, insulin pump, implantable cardioverter defibrillator, neurostimulators).<br>6. Individuals with a current/recent diagnosis or symptoms of SARS-CoV-2 were not invited to visit the university until it was safe for them to do so (2 weeks following positive test).<br>7. Diagnosis of non-verbal autism or similar condition which would affect the ability to give informed consent to take part in the study.<br>8. Pregnant women.<br>9. Participants who have participated in previous research studies involving median nerve stimulation.<br>10. Participants aged over 90 years old. |

Note. RCT, randomised controlled trial; YGTSS, Tale Global Tic Severity Scale; HRT, habit reversal therapy; ERP, exposure and response prevention; CBIT, comprehensive behavioural intervention for tics; TS, Tourette Syndrome; CTD, chronic tic disorder

## Appendix 3 Completed quality assessment forms for included studies

### Table 29 Philips checklist quality assessment of ORBIT study

| Dimension of quality | Questions for critical appraisal | Assessment | Reviewer comments |
|---|---|---|---|
| **Statement of decision problem/objective** | *Is there a clear statement of the decision problem?* | Y | None |
| | *Is the objective of the evaluation and model specified and consistent with the stated decision problem?* | N | The objective of the evaluation is clearly described and relevant to the context of the decision problem for the study. However, the comparator for the evaluation (online psychoeducation, including use of the BiP intervention platform) may not align closely with the decision problem for the NICE medtech assessment (face-to-face behavioural therapy). |
| | *Is the primary decision-maker specified?* | Y | |
| **Statement of scope/perspective** | *Is the perspective of the model stated clearly?* | Y | |
| | *Are the model inputs consistent with the stated perspective?* | Y | |
| | *Has the scope of the model been stated and justified?* | Y | |
| | *Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?* | Y | |
| **Rationale for structure** | *Has the evidence regarding the model structure been described?* | Y | |
| | *Is the structure of the model consistent with a coherent theory of the health condition under evaluation?* | Y | Yes, but there is uncertainty surrounding the link between YGTSS-TTSS score and health state utilitiy |

| Dimension of quality | Questions for critical appraisal | Assessment | Reviewer comments |
|---|---|---|---|
| | | | values that requires further investigation. That being said, the model structure is coherent and plausible. |
| | *Have any competing theories regarding model structure been considered?* | N | No alternatives (such as linear relationship between tic severity and utility) have been proposed. Similarly, no discussion around whether the categorisation based on YGTSS_TTSS is the most appropriate definition. Clinical expert validation would have been helpful. |
| | *Are the sources of data used to develop the structure of the model specified?* | Y | Briefly mentioned. |
| | *Are the causal relationships described by the model structure justified appropriately?* | Y | Yes, however there is some uncertainty. |
| **Structural assumptions** | *Are the structural assumptions transparent and justified?* | Y | |
| | *Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?* | Partly | Structural assumptions imply that transition probabilities can be extrapolated indefinitely beyond the trial observation endpoint. There is no evidence to support or refute this assumption and further scenario analyses would have been useful. |
| **Strategies/comparators** | *Is there a clear definition of the options under evaluation?* | Y | |
| | *Have all feasible and practical options been evaluated?* | Y | |
| | *Is there justification for the exclusion of feasible options?* | N/A | |

| Dimension of quality | Questions for critical appraisal | Assessment | Reviewer comments |
|---|---|---|---|
| **Model type** | *Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?* | Y | |
| **Time horizon** | *Is the time horizon of the model sufficient to reflect all important differences between options?* | N | A time horizon of 10 years was used, but this may be appropriate given uncertainties surrounding long-term extrapolations. |
| | *Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?* | N | The duration of treatment effect is assumed to be indefinite, despite no ongoing intervention costs being incurred. Further justification of this assumption would have been helpful. |
| | *Has a lifetime horizon been used? If not, has a shorter time horizon been justified?* | N | Not explicitly justified but may be appropriate given the uncertainty in long-ter extrapolations beyond the trial observation follow-up. |
| **Disease states/pathways** | *Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?* | Y | |
| **Cycle length** | *Is the cycle length defined and justified in terms of the natural history of disease?* | Y | |
| **Data identification** | *Are the data identification methods transparent and appropriate given the objectives of the model?* | Partly | The model was informed by trial data, though it was not always possible to follow what methods were used to derive model input parameters (e.g. were annual transitions appropriate converted to six-month cycle specific transitions, data to support the exclusion of particular health state costs categories would have been helpful). |

| Dimension of quality | Questions for critical appraisal | Assessment | Reviewer comments |
|---|---|---|---|
| | *Where choices have been made between data sources, are these justified appropriately?* | N | No details provided. |
| | *Has particular attention been paid to identifying data for the important parameters in the model?* | Y | data obtained from the trial (best available data). |
| | *Has the process of selecting key parameters been justified and systematic methods used to identify the most appropriate data?* | N | Systematic methods have not been clearly documented. |
| | *Has the quality of the data been assessed appropriately?* | N | There is a lack of quality assessment of the input data, in particular small counts for transition probabilities from the trial. |
| | *Where expert opinion has been used, are the methods described and justified?* | N | |
| **Premodel data analysis** | *Is the data analysis (premodel) methodology based on justifiable statistical and epidemiological techniques?* | Y | |
| **Baseline data** | *Is the choice of baseline data described and justified?* | Y | |
| | *Are transition probabilities calculated appropriately?* | Unclear | However, it is unclear how annual transitions were converted to six-month cycle specific transitions |
| | *Has a half-cycle correction been applied to both cost and outcome?* | N | Use of a half cycle correction has not been reported. Assume not applied. |
| | *If not, has this omission been justified?* | N | |
| **Treatment effects** | *If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?* | Y | Data from one trial applied in the model. Raw data parameterised in each arm is appropriate but does not include exploration of correlated draws for each arm. |

| Dimension of quality | Questions for critical appraisal | Assessment | Reviewer comments |
|---|---|---|---|
| | *Have the methods and assumptions used to extrapolate shortterm results to final outcomes been documented and justified? Have alternative assumptions been explored through sensitivity analysis?* | N | The methods are not clearly described, though it appears that last observed transition probabilities are carried forwards. This assumption is not well justified, particularly given that intervention costs do not appear to be applied beyond 18 months (trial observation period). no sensitivity or scenario analyses have been conducted to explore this uncertainty. |
| | *Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified? Have alternative assumptions been explored through sensitivity analysis?* | N | As described above. |
| **Quality of life weights (utilities)** | *Are the utilities incorporated into the model appropriate? Is the source for the utility weights referenced?* | Partly | It is unclear whether parent reported proxy or child self-reported responses to the CHU-9D are used. |
| | *Are the methods of derivation for the utility weights justified?* | Y | based on published literature. Unclear if utilities are age adjusted in the model though this likely would have minimal impact for a cohort at starting age 12 over 10 years. |
| **Data incorporation** | *Have all data incorporated into the model been described and referenced in sufficient detail?* | Y | |
| | *Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?* | Unclear | |
| | *Is the process of data incorporation transparent?* | Y | |
| | *If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?* | Y | |
| | *If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?* | Y | |

| Dimension of quality | Questions for critical appraisal | Assessment | Reviewer comments |
|---|---|---|---|
| **Assessment of uncertainty** | *Have the four principal types of uncertainty been addressed?* | N | Long-term extrapolation (continuing treatment effect beyond intervention delivery) is not explored in scenario analyses. Similarly, any long-term intervention costs required to generate effectiveness are not explored. |
| | *If not, has the omission of particular forms of uncertainty been justified?* | N | |
| **Methodological** | *Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?* | N | |
| **Structural** | *Is there evidence that structural uncertainties have been addressed via sensitivity analysis?* | N | |
| **Heterogeneity** | *Has heterogeneity been dealt with by running the model separately for different subgroups?* | N | Although it is difficult to see how to appropriately parameterise subgroups in this case. |
| **Parameter** | *Are the methods of assessment of parameter uncertainty appropriate?* | Y | |
| | *Has probabilistic sensitivity analysis been done? If not, has this been justified?* | Y | |
| | *If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?* | Y | |
| **Internal consistency** | *Is there evidence that the mathematical logic of the model has been tested thoroughly before use?* | N | |
| **External consistency** | *Are the conclusions valid given the data presented?* | Y | Although uncertainty is likely understated. |
| | *Are any counterintuitive results from the model explained and justified* | N/A | |

| Dimension of quality | Questions for critical appraisal | Assessment | Reviewer comments |
|---|---|---|---|
| | *If the model has been calibrated against independent data, have any differences been explained and justified?* | N | |
| | *Have the results of the model been compared with those of previous models and any differences in results explained?* | N/A | First model in this area. |

## Appendix 4 Additional cost-effectiveness results for ORBIT vs. online psychoeducation

**Table 30 Scenario analyses for comparison of ORBIT vs. online psychoeducation (deterministic)**

| S. No | Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) |
|---|---|---|---|---|---|---|
| **0** | **Base case** | | | | | |
| | Psychoeducation | £12,755 | 20.916 | - | - | - |
| | ERP | £12,974 | 20.939 | £218 | 0.024 | £9,289 |
| **1** | **Time horizon = 10 years from end of trial follow-up (18 months + 10 years)** | | | | | |
| | Psychoeducation | £5,128 | 7.738 | - | - | - |
| | ERP | £5,397 | 7.767 | £269 | 0.028 | £9,490 |
| **2** | **Times horizon = 5 years from end of trial follow-up (18 months + 5 years)** | | | | | |
| | Psychoeducation | £3,422 | 4.593 | - | - | - |
| | ERP | £3,702 | 4.623 | £280 | 0.030 | £9,451 |
| **3** | **Time horizon = 2 years from end of trial follow-up (18 months + 2 years)** | | | | | |
| | Psychoeducation | £2,253 | 2.413 | - | - | - |
| | ERP | £2,540 | 2.443 | £287 | 0.030 | £9,584 |
| **4** | **Include transitions into the absorbing 'tics free' health state, set utility tics free = mild** | | | | | |
| | Psychoeducation | £5,955 | 21.305 | - | - | - |
| | ERP | £6,219 | 21.327 | £264 | 0.022 | £12,254 |
| **5** | **Include only variable cost of therapist support for psychoeducation** | | | | | |
| | Psychoeducation | £12,513 | 20.916 | - | - | - |
| | ERP | £12,974 | 20.939 | £460 | 0.024 | £19,582 |

| S. No | Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) |
|---|---|---|---|---|---|---|
| **6** | **Apply approach from ORBIT study (include only variable platform costs and therapist support for psychoeducation; remove all ongoing costs)** | | | | | |
| | Psychoeducation | £12,520 | 20.916 | - | - | - |
| | ERP | £12,830 | 20.939 | £311 | 0.024 | £13,216 |
| **7** | **Only include variable therapist support costs, include ongoing costs + platform throughput (n=100)** | | | | | |
| | Psychoeducation | £12,631 | 20.916 | - | - | - |
| | ERP | £13,026 | 20.939 | £396 | 0.024 | £16,831 |
| **8** | **Only include variable therapist support costs, include ongoing costs + platform throughput (n=1000)** | | | | | |
| | Psychoeducation | £12,631 | 20.916 | - | - | - |
| | ERP | £12,940 | 20.939 | £310 | 0.024 | £13,172 |
| **9** | **Remove ongoing intervention costs from both arms (i.e. no variable costs applied for each cycle)** | | | | | |
| | Psychoeducation | £12,638 | 20.916 | - | - | - |
| | ERP | £12,830 | 20.939 | £192 | 0.024 | £8,177 |
| **10** | **Remove long-term transition probabilities (retain in state beyond 18 months), assumes 18-month benefit retained indefinitely** | | | | | |
| | Psychoeducation | £12,646 | 20.870 | - | - | - |
| | ERP | £12,722 | 20.989 | £76 | 0.119 | £640 |
| **11** | **ERP transition probabilities revert to online psychoeducation arm after 18 months** | | | | | |
| | Psychoeducation | £12,755 | 20.916 | - | - | - |
| | ERP | £13,040 | 20.948 | £284 | 0.033 | £8,747 |
| **12** | **Apply additional medication costs to moderate and severe health states** | | | | | |
| | Psychoeducation | £13,466 | 20.916 | - | - | - |
| | ERP | £13,717 | 20.939 | £251 | 0.024 | £10,695 |

**Abbreviations:** QALY, quality adjusted life years; ICER, incremental cost-effectiveness ratio;ERP, Exposure and response prevention

**Table 31 Scenario analyses for comparison of Neupulse vs. waitlist control (deterministic)**

| S. No | Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) |
|---|---|---|---|---|---|---|
| **0** | **Base case** | | | | | |
| | Wait list control | £7,693 | 19.138 | - | - | - |
| | Neupulse | [redacted] | 19.765 | [redacted] | 0.627 | [redacted] |
| **1** | **Time horizon = 10 years** | | | | | |
| | Wait list control | £2,749 | 6.938 | | | |
| | Neupulse | [redacted] | 7.158 | [redacted] | 0.220 | [redacted] |
| **2** | **Times horizon = 5 years** | | | | | |
| | Wait list control | 1,548 | 3.752 | | | |
| | Neupulse | [redacted] | 3.865 | [redacted] | 0.113 | [redacted] |
| **3** | **Time horizon = 2 years** | | | | | |
| | Wait list control | £695 | 1.537 | | | |
| | Neupulse | [redacted] | 1.575 | [redacted] | 0.038 | [redacted] |
| **4** | **Include transitions into the absorbing 'tics free' health state, set utility tics free = mild** | | | | | |
| | Wait list control | £3,258 | 19.486 | - | - | - |
| | Neupulse | [redacted] | 19.766 | [redacted] | 0.280 | [redacted] |
| **5** | **Long-term transition probabilities: set equal to zero, assumes no further improvement of regression of tics and TS after 4 weeks** | | | | | |

| S. No | Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) |
|---|---|---|---|---|---|---|
| | Wait list control | £10,707 | 18.659 | - | - | - |
| | Neupulse | [redacted] | 18.763 | [redacted] | 0.103 | [redacted] |
| **6** | **Long-term transition probabilities: assume that Neupulse cohort reverts to 'no treatment' transition matrix after 4 weeks** | | | | | |
| | Wait list control | £7,693 | 19.138 | - | - | - |
| | Neupulse | [redacted] | 19.157 | [redacted] | 0.019 | [redacted] |
| **7** | **Apply additional medication costs to moderate and severe health states** | | | | | |
| | Wait list control | £8,563 | 19.138 | | | |
| | Neupulse | [redacted] | 19.765 | [redacted] | 0.627 | [redacted] |

**Abbreviations:** QALY, quality adjusted life years; ICER, incremental cost-effectiveness ratio

NoACIC

# GID-MT605 Digitally enabled therapy for chronic tic disorders and Tourette syndrome

Health technologies advisory committee: 15 August 2024


**Committee introducers:** Stacey Chang-Douglass, Tara Murphy

**Lay SCMs:** Emma McNally, Joanne Dooley, Samantha Bramley

**External assessment group:** Aberdeen Health Technology Assessment Group

**Technical team:** Kimberley Carter, Ziqi Zhou


NICE National Institute for Health and Care Excellence

# Digitally enabled therapy for tic disorder

The following slides provide an overview of the external assessment group (EAG) report for this topic. Not all these slides will be presented at the committee meeting but the main information in this set of slides will be summarised. We have tried not to repeat information found in the other documents and references can be found in the slide notes.

Key documents in this assessment include:

- The final scope - contains the decision problem for the assessment
- The external assessment report (EAR)* - assessment of the included technologies by the EAG. The report has a more detailed executive summary which provides an overview of the EAG's work and links to the relevant sections of the report.

The slides contain information that has been supplied in confidence. Academic in confidence information is underlined and highlighted in yellow and commercial in confidence information in blue



* These documents are in the Committee pack and will be published at consultation

# Technology purpose and unmet need

Accepted evidence-based treatment options for diagnosed tic disorders are psychoeducation as a first line option and behavioural therapies for those who continue to report difficulties with their tic disorder.

Behavioural therapies for tic disorders include habit reversal therapy, comprehensive behavioural intervention for tics (CBIT) and exposure and response prevention therapy (ERP).

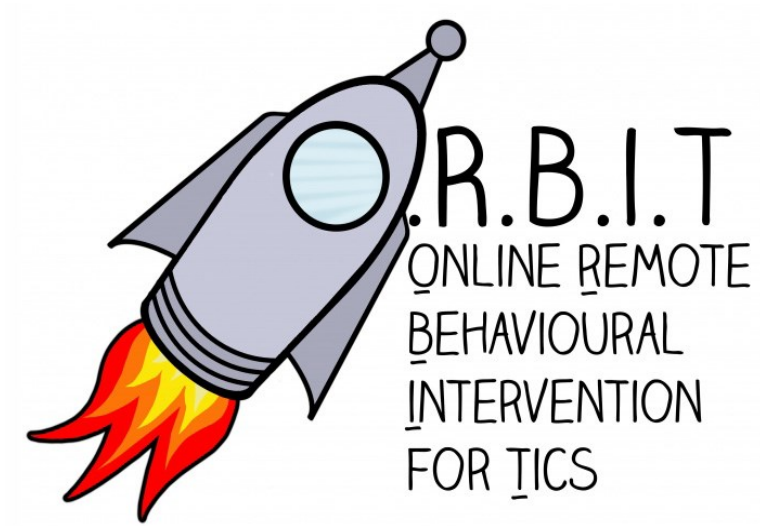
Due a shortage of trained therapists, behavioural therapy is being offered at a small number of specialist treatment centres. As a result, experts estimate less than 20% of children and young people with tic disorders currently have access to behavioural therapies (Marino et al, 2023).

Digital technologies that enable the remote/online delivery of therapeutic intervention are considered.

The aim of the digitally enabled therapy is to improve access as well as equity of access to treatment options for people with chronic tic disorders and Tourette syndrome due to varied expertise, access and availability of services across the UK.

# The technologies

1) Online Remote Behavioural Intervention for Tics (ORBIT)
    - developed from an existing research platform (BIP TIC) in Sweden
    - age-appropriate in appearance for use by children and their parents and includes animations and interactive scripts
    - MHRA has determined that ORBIT is not a medical device



# The technologies

## 2) Neupulse

- a novel approach to reduce tic frequency and severity
- a wearable wrist-worn neuromodulation device with a corresponding phone app
- addresses the imbalances in neural activity which are associated with tics and premonitory urges by modulating neural oscillations within the brain’s sensorimotor networks
- working towards CE and UKCA marking, and it is estimated that the device will be available in 2026

# Summary of technologies

| Technology (Company) | ORBIT (Mindtech) | Neupulse (Neurotherapeutics) |
|---|---|---|
| Platform | Delivered remotely via the BIP (Barninternetprokektet, Swedish for Child Internet Project) technical platform.<br>Can be accessed via the internet using a smartphone, desktop computer or laptop. | Wrist worn stimulation device |
| Methods | Exposure and response prevention (ERP).The intervention is delivered in 10 chapters split into child intervention and parent/supporter intervention. | Transcutaneous electrical stimulation (TENS) to the median nerve stimulation at a frequency of 10Hz with intensity levels (1-14mA) adjustable via a mobile phone App. |
| Aim of therapy | ERP aims to break the urge-tic-relief cycle of reinforcement whilst promoting tolerance of premonitory urges and tic suppression | Immediate reduction of urge to tic and tic intensity |
| Duration | 10 weeks | Intermittent on demand (1 hr session) up to 8 hours depending on battery life |
| Contact with therapist | Remote contact; at least once a week via messages sent inside the treatment platform (resembling an email). | Over the counter – no prescription required.<br>No contact with therapist is required<br>App can collate symptom monitoring data for review by a HCP |

# Condition and patient group (1)

- Tic disorders are neurodevelopmental conditions characterised by fast, irregular, and repetitive muscle movements that can manifest in any part of the body.
- Tics that affect body movements (e.g., blinking, grimacing, head jerking, head banging, finger clicking) are known as motor tics, while involuntary repetitive sounds, such as grunting, sniffing, or throat clearing are known as vocal or phonic tics.
- There are different types of tic disorders according to their manifestation and frequency.
    - Transient or provisional tic disorders: tics present for less than 12 months since the first tic onset
    - Persistent or chronic tic disorders: tics persist for more than 12 months since the first tic onset
- Tourette syndrome refers to multiple motor tics and one or more vocal tics that have been present at the same time (but not necessarily concurrently) during the course of the disease and have persisted for more than 12 months since the first tic onset.
- In the UK, Tourette Syndrome is identified in 1 per 100 school children.

# Condition and patient group (2)

- The mean age of onset for tic disorders is approximately 5 years, although it can be lower in up to 40% of patients.
- Typically, the severity of tic disorders worsens between 10 and 12 years of age and improves naturally during adolescence and early adulthood.
- Psychiatric comorbidities are common among people who suffer from chronic tic disorders, such as ADHD (30 to 54% of people) and OCD (10% to 50% of people). Tourette syndrome has also been reported to be associated with an increased risk of anxiety.
- In all cases, onset is before the age of 18 years and the tics are not attributable to the physiological effects of a substance (e.g., cocaine) or other medical conditions (e.g., Huntington’s Disease, post-viral encephalitis).
- Tic disorders can vary in severity and impact various aspects of people's lives, contributing to a reduced quality of life.
- Severe long-lasting tic disorders are also associated with a fourfold increased risk of suicide.



ADHD: attention deficit hyperactivity disorder

OCD: obsessive-compulsive disorder

# Decision problem

| PICO | |
|---|---|
| Population | Children, young people and adults with chronic tic disorders or Tourette Syndrome. |
| *Subgroups* | • Children and young people with diagnosed comorbidities, including: attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), autism spectrum disorder (ASD), mood disorders, and anxiety.<br>• Adults with chronic tic disorders |
| Interventions | Digitally enabled technologies for the treatment of people with chronic tic disorders:<br>• Online Remote Behavioural Intervention for Tics (ORBIT)<br>• Neupulse |
| Comparator | Standard care, including psychoeducation and face-to-face behavioural therapy. |
| Key Outcomes | • Intermediate outcome measures<br>• Clinical outcome measures<br>• Patient-reported outcomes<br>• Costs (from NHS and Personal Social Services perspective) |



For full decision problem see the final scope

# Current management (1)

- In the UK, people with tic disorders attend an initial appointment with a general practitioner (GP) working in primary care. When the presence of a tic disorder is recognised to have a significant impact on people's quality of life, a referral is usually made to appropriate secondary or tertiary care services (depending on the presentation, comorbidities, and local specialist clinics).
- For children and young people, referrals may be made to mental health services neurodevelopmental teams, paediatric or neurology teams dependent on local services. For adults, referrals are usually made to neurological services.
- The NICE Guideline (NG127) indicates that
  - ❑ children or young people with tic disorders, that significantly interfere with their ability to function in their daily lives, should be referred to specialist mental health services, neurodevelopmental teams or for neurological assessment.
  - ❑ adults with tic disorders should be considered for neurological assessment if their symptoms are severe and the disorder continues to cause distress.
  - ❑ as tics may improve with time, for individuals presenting in primary care a watch-and-wait approach is considered acceptable, especially for those who do not experience any functional impairment.

# Current management (2)

Treatment options for chronic tic disorders include psychoeducation, behavioural therapy, pharmacological therapy, and deep brain stimulation.

1) Psychoeducation
    - aims to reduce stigma and distress and increase awareness of the illness
    - the initial approach to treating all tic disorder
    - rarely provided by general practitioners in the first appointment

2) Behavioural therapy
    - the first-line intervention for tic disorders in both children and young people and adults
    - more robust evidence of efficacy are habit reversal training (HRT), comprehensive behavioural intervention for tics (CBIT) and the efficacy of exposure with response prevention (ERP)
    - due to a shortage of trained therapists, behavioural therapy is only available in a small number of specialist centres and only about 20% of people with tic disorders have access to it

# Current management (3)

3) Pharmacological therapy

- some evidence that a2-adrenergic receptor agonists (e.g., clonidine, guanfacine) and antipsychotic drugs (e.g., risperidone, haloperidol) are effective in the short term
- mostly considered for the treatment of severe tics when a2-adrenergic receptor agonists are not effective or not tolerated
- the decision about the type and dosage of pharmacological therapy should be provided by a health professional

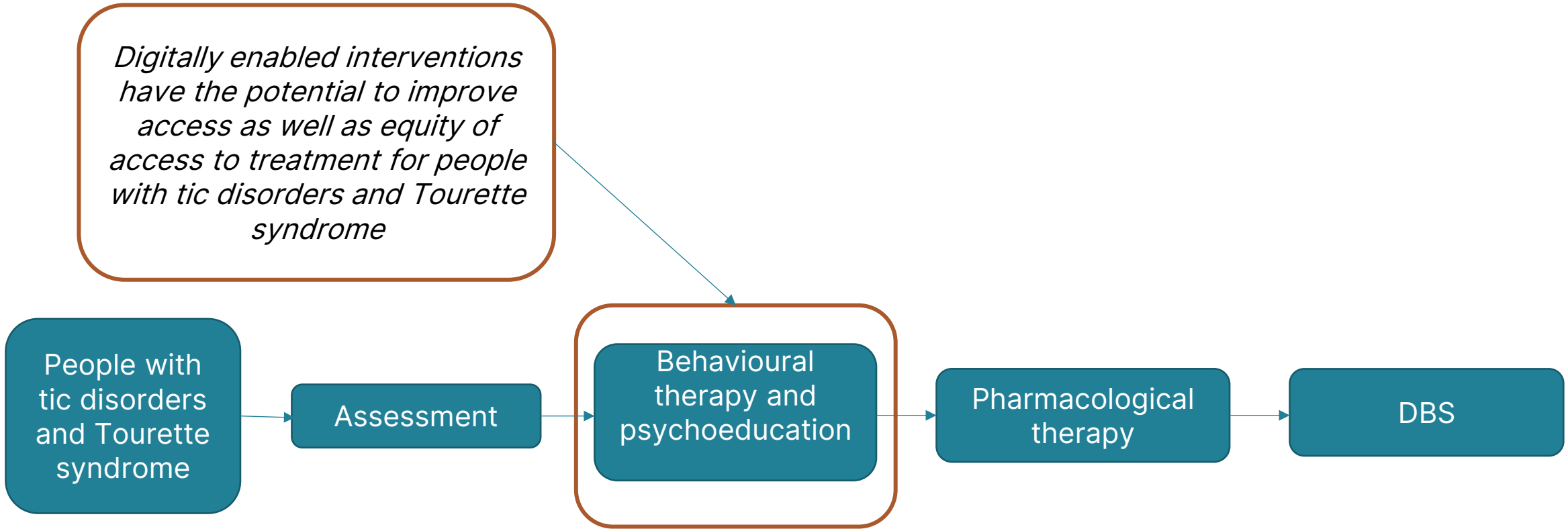
4) Deep brain stimulation (DBS)

- for patients with severe tics that are refractory to behavioural and pharmacological interventions in specialised centres
- little information on the effects of DBS in children and young people with chronic tic disorders to support its use in clinical practice

❑ Alternative treatments such as dietary supplements, fish oils, acupuncture and antibiotics have also been proposed for tic disorders, but the rationale and evidence of their efficacy is still unclear or insufficient.

❑ Novel treatment options such as median nerve stimulation (MNS) are currently under investigation.

# Care pathway






DBS: Deep brain stimulation

# Patient organisation submission: Tourettes Action

The NHS currently has no pathway for a TS assessment and diagnosis and accessing support can take many years. Full clinical guidelines and fully resourced services are needed for full benefit to be achieved.

There are huge regional variations in care.

The impact of tics and TS can have a huge life-long impact on people's ability to lead a normal life due to pain, stigma, isolation and anxiety, affecting education, employment and both physical, emotional and mental health.

TS causes an adverse impact on family life, i.e. parental employment, family finances, socialisation, sibling and family isolation and dysfunctional family dynamics.

The impact of additional needs and co-occurring conditions on the mental and physical wellbeing of people with TS across the lifespan needs to be considered.



For further details see the full Tourettes Action submission included in the pack

# Equality and diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

- Tic disorders manifest more often in boys than girls with a ratio between 3:1 and 4:1.
- In the UK, Tourette Syndrome is identified in 1 per 100 school children. The mean age of onset for tic disorders is approximately 5 years, although it can be lower in up to 40% of patients. Typically, the severity of tic disorders worsens between 10 and 12 years of age and improves naturally during adolescence and early adulthood.
- People with tic disorders, particularly when the illness is more severe, will experience serious social issues such as extensive stigma, public avoidance and discrimination.
- Age, disability, race and religion and belief are protected characteristics under the Equality Act (2010).

# Equality and diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

- Digitally enabled technologies for tic disorders and Tourette syndrome are accessed via a mobile phone, tablet, or computer. People will need regular access to a device with internet access to use the technologies. Additional support and resources may be needed for people who are unfamiliar with digital technologies or do not have access to smart devices or the internet.
- People with cognitive impairment, problems with manual dexterity , learning disabilities or who have difficulty reading or understanding health-related information may need additional support to use digital technologies.
- People's ethnic, religious, and cultural background may affect their views of digital interventions.

# Clinical evidence summary

- A total of three RCTs were included in the review of clinical effectiveness.
- Two studies compared ORBIT with psychoeducation; one was conducted in the UK (Hollis 2021) and the other in Sweden (Andren 2022). The two ORBIT studies recruited children and young people aged 9 to 17 years.(Hollis 2021, Andren 2022).
- The third study was UK-based and compared Neupulse active stimulation with sham stimulation; this trial also included an open-label waitlist (treatment as usual) control condition which is reported here for completeness. (Maiquez 2023). The Neupulse study recruited people aged 12 years upwards.(Maiquez 2023).

# Characteristics of included studies (1)

| Study ID | Intervention group (n analysed) | Age, years, mean (SD) | Male sex, % | Tic typology, % | Comorbidities, % |
|---|---|---|---|---|---|
| Hollis 2021 (ORBIT UK) | ERP (n=112) | 12.2 (2.0) | 80.4 | Both motor and vocal tics: 92%<br>Motor tics only: 8%<br>Vocal tics only: 0% | Anxiety disorder: 30%<br>ADHD: 23%<br>Oppositional defiant disorder: 24% [n=110]<br>Autism spectrum disorder: 8%[n=111]<br>OCD: 7%<br>Major depression: 2%<br>Conduct disorder: 3% [n=110] |
| | Psychoeducation (n=112) | 12.4 (2.1) | 77.7 | Both motor and vocal tics: 95%<br>Motor tics only: 5%<br>Vocal tics only: 0% | Anxiety disorder: 24%<br>ADHD: 22%<br>Oppositional defiant disorder: 21% [n=111]<br>Autism spectrum disorder: 4%<br>OCD: 3%<br>Major depression: 5%<br>Conduct disorder: 2% [n=111] |

ERP: exposure and response prevention; ADHD: attention deficit hyperactivity disorder; OCD: obsessive compulsive disorder.

# Characteristics of included studies (2)

| Study ID | Intervention group (n analysed) | Age, years, mean (SD) | Male sex, % | Tic typology, % | Comorbidities, % |
|---|---|---|---|---|---|
| Andren 2022 (ORBIT Sweden) | ERP (n=111) | 12.0 (2.3) | 64.0 | Tourette syndrome: 93.7%<br>Chronic tic disorder motor: 6.3%<br>Chronic tic disorder vocal: 0% | Any: 39.6%<br>ADHD: 18.0%<br>Anxiety disorder: 14.4%<br>OCD: 9.9%<br>Depression: 0.9%<br>Other: 6.3% |
| | Education (n=110) | 12.1 (2.3) | 73.6 | Tourette syndrome: 89.1%<br>Chronic tic disorder motor: 8.2%<br>Chronic tic disorder vocal: 2.7% | Any: 36.0%<br>ADHD: 12.7%<br>Anxiety disorder: 13.6%<br>OCD: 5.5%<br>Depression: 2.7%<br>Other: 2.7% |



ERP: exposure and response prevention; ADHD: attention deficit hyperactivity disorder; OCD: obsessive compulsive disorder.

# Characteristics of included studies

| Study ID | Intervention group (n analysed) | Age, years, mean (SD) | Male sex, % | Tic typology, % | Comorbidities, % |
|---|---|---|---|---|---|
| Maiquez 2023 (Neupulse) | Active stimulation (n=41) | 23.5 (12.6) | 63.4 | NR | ADHD: 24.4%<br>OCD: 41.5%<br>Autism spectrum disorder: 19.5%<br>Anxiety disorder: 22.0% |
| | Sham stimulation (n=39) | 24.0 (13.4) | 59.0 | NR | ADHD: 23.1%<br>OCD: 20.5%<br>Autism spectrum disorder: 23.1%<br>Anxiety disorder: 30.8% |
| | Waitlist (n=41) | 24.4 (12.6) | 63.4 | NR | ADHD: 19.5%<br>OCD: 29.3%<br>Autism spectrum disorder: 4.9%<br>Anxiety disorder: 26.8% |



NR: Not reported

# Clinical evidence: EAG critique of evidence

| Study ID | Experimental | Comparator | Randomisation process | Deviations from intended | Missing outcome data | Measurement of the outcome | Selection of the reported results | Overall |
|---|---|---|---|---|---|---|---|---|
| Hollis 2021 | ERP | Psychoeducation | + | + | + | + | + | + |
| Andren 2022 | ERP | Education | + | + | + | + | + | + |
| Maiquez 2023 | Active stimulation | Sham stimulation | + | + | + | + | + | + |

+ Low risk

! Some concerns

- High risk

According to the Cochrane risk of bias tool (version 2), the overall risk of bias was low for the three trials (Hollis 2021, Andren 2022, Maiquez 2023).

# Clinical evidence: ORBIT meta-analysis

- Meta-analysis results of the two ORBIT studies (Hollis 2021 & Andren 2022) showed that tic severity in terms of YGTSS-TTSS scores was significantly lower in children and young people in the ERP groups than those in the psychoeducation groups at 3 months and 12 months. No significant differences in tic-related impairment measured using the YGTSS impairment scale were observed between treatment groups.

| Meta-analysis | Time point (months) | ERP | Psychoeducation | Mean difference | Heterogeneity |
|---|---|---|---|---|---|
| YGTSS-TTSS | 3 | 212 | 210 | -2.12 [-3.52, -0.73] (p=0.003) | $I^2$=0% |
| | 12 | 198 | 192 | -2.45 [-4.05, -0.85] (p=0.003) | $I^2$=0% |
| YGTSS-Impairment | 3 | 209 | 208 | -1.53 [-3.32, 0.26] (p=0.09) | $I^2$=0% |
| | 12 | 198 | 192 | -0.90 [-3.90, 2.10] (p=0.56) | $I^2$=57% |



ERP: exposure and response prevention; YGTSS-TTSS: Yale Global Tic Severity Scale – Total Tic Severity Score

# Clinical evidence: ORBIT clinical outcomes (1)

The primary outcome of all three studies was total tic severity assessed by the YGTSS-TTSS scale in the two ORBIT studies and by a revised version of the YGTSS-TTSS scale in the Neupulse study.

| YGTSS-TTSS data reported in the two ORBIT studies | | | | | |
|---|---|---|---|---|---|
| Study | | Difference between groups at time point | | | |
| | | 3 months | 6 months | 12 months | 18 months |
| Hollis 2021 (ORBIT UK) | Estimated difference | -2.29 (-3.86, -0.71) | -2.64 (-4.56, -0.73) | -2.64 (-4.48, -0.79) | -2.01 (-3.86, -0.15) |
| | Effect size | -0.31 (-0.52, -0.10) | -0.36 (-0.62, -0.10) | -0.36 (-0.61, -0.11) | -0.27 (-0.52, -0.02) |
| Andren 2022 (ORBIT Sweden) | | ITT linear quantile mixed model coefficient: -0.53 (-1.28, 0.22) Effect size: 0.11 (-0.09, 0.30), p=0.17 | NR | Interaction between treatment and time coefficient: -0.38 (-1.11, 0.35), p=0.30 Effect size: 0.13 (-0.12, 0.37) | |

# Clinical evidence: ORBIT clinical outcomes (2)

Clinical outcome measures from two ORBIT studies (Hollis 2021 & Andren 2022)include YGTSS-Impairment, Parent tic questionnaire (PTQ), Clinical Global Impressions – Improvement Scale (CGI-I), Clinical Global Impression Severity scale (CGI-S), Children's Global Assessment Scale (CGAS) and strengths and difficulties questionnaire.

In each ORBIT study, secondary outcome measures such as the CGAS did not show a greater response in the ERP group compared to the psychoeducation group.

| Children's Global Assessment Scale (CGAS) | | | | | |
|---|---|---|---|---|---|
| Study | | Difference between groups at time point | | | |
| | | 3 months | 6 months | 12 months | 18 months |
| Hollis 2021 (ORBIT UK) | Estimated difference | 0.96 (-1.48, 3.41) | 0.60 (-2.24, 3.44) | 2.85 (0.15, 5.56) | 3.18 (0.47, 5.90) |
| | Effect size | 0.08 (-0.12, 0.27) | 0.05 (-0.17, 0.27) | -0.22 (-0.43, -0.01)** | -0.25 (-0.46, -0.04)** |
| Andren 2022 (ORBIT Sweden) | Coefficient | 0.67 (-0.15, 1.49), p=0.11, effect size | | | |
| | Effect size | 0.12 (-0.05, 0.29) | | | |



**p<0.05. data reported as mean (SD)

# Clinical evidence: ORBIT clinical outcomes (3)

The estimated mean difference in the Parent Tic Questionnaire at 3 months favoured the ERP group in the UK ORBIT study but not in the Swedish ORBIT study.

| Parent tic questionnaire (PTQ) | | | | | |
|---|---|---|---|---|---|
| Study | | Difference between groups at time point | | | |
| | | 3 months | 6 months | 12 months | 18 months |
| Hollis 2021 (ORBIT UK) | Estimated difference | -9.44 (-15.37, -3.51) | -8.60 (-14.43, -2.77) | -9.89 (-16.01, -3.77) | -2.15 (-8.83, 4.53) |
| | Effect size | -0.34 (-0.55, -0.13) | -0.31 (-0.51, -0.10) | -0.35 (-0.57, -0.13) | -0.08 (-0.31, 0.16) |
| Andren 2022 (ORBIT Sweden) | Coefficient | ITT linear quantile mixed model coefficient: 0.13 (-1.43, 1.68) Effect size: -0.01 (-0.22, 0.19) p=0.87 | NR | Interaction between treatment and time coefficient: -0.10 (-1.63, 1.44), p=0.90 Effect size: 0.02 (-0.22, 0.26) | |

# Clinical evidence: ORBIT clinical outcomes (4)

At 3 months, participants in the ERP group showed better CGI-I results in the UK ORBIT study and better CGI-S results in the Swedish ORBIT study. Other measures evaluating mood, emotional, and behavioural functioning showed similar responses in both the ERP and psychoeducation groups.

| Clinical Global Impressions – Improvement Scale (CGI-I) | | | | | |
|---|---|---|---|---|---|
| Study | | Difference between groups at time point | | | |
| | | 3 months | 6 months | 12 months | 18 months |
| Hollis 2021 (ORBIT UK) | Estimated difference | -0.41 (-0.71, -0.11) | -0.31 (-0.66, 0.03) | -0.43 (-0.75, -0.10) | -0.38 (-0.71, -0.05) |
| | Effect size | -0.37 (-0.64, -0.10) | -0.29 (-0.61, 0.03) | -0.43 (-0.74, -0.12) | -0.35 (-0.66, -0.04) |
| **Clinical Global Impression Severity scale (CGI-S)** | | | | | |
| Andren 2022 (ORBIT Sweden) | | ITT linear quantile mixed model coefficient: -0.36 (-0.67, -0.04), p=0.03<br>Effect size: 0.71 (0.05, 1.37) | NR | Interaction between treatment and time coefficient: 0.03 (-0.16, 0.21), p=0.28<br>Effect size: -0.11 (-0.80, 0.58) | |

# Clinical evidence: ORBIT patient reported outcomes

- Health-related quality of life outcomes were reported in child and adolescent Gilles de la Tourette quality of life scale (C&A-GTS-QOL) scores reported.
- There were mixed results across studies.

| Study | | Difference between groups at time point | | | |
|---|---|---|---|---|---|
| | | 3 months | 6 months | 12 months | 18 months |
| Hollis 2021 (ORBIT UK) | Estimated difference | -4.81 (-8.79, -0.83) | -2.91 (-7.60, 1.78) | -5.79 (-10.28, -1.30) | -9.00 (-13.98, -4.01) |
| | Effect size | -0.29 (-0.52, -0.05) | -0.17 (-0.45, 0.11) | -0.34 (-0.61, -0.08) | -0.53 (-0.83, -0.24) |
| Andren 2022 (ORBIT Sweden) | Coefficient | 0.46 (-1.63, 2.55), p=0.67 | NR | 0.18 (-0.98, 1.33), p=0.77 | |



C&A-GTS-QOL, child and adolescent Gilles de la Tourette quality of life scale

# Clinical evidence: Neupulse clinical outcomes

The Neupulse study reported lower YGTSS-TTSS scores at 4 weeks in the active stimulation group compared to the sham stimulation group with the difference being statistically significant.

| Study | Time point | Active stimulation | Sham stimulation | Waitlist | Difference between groups at time point |
|---|---|---|---|---|---|
| Maiquez 2023 (Neupulse) | Baseline | 40.1 (7.0) | 39.5 (6.3) | 38.9 (6.9) | N/A |
| | 4 weeks | Mean (SD) reduction | Mean (SD) reduction | Mean (SD) reduction | Active vs sham: Observed difference -5, effect size -0.47 (-0.94, -0.02), p=0.02 |
| | | 7.13 (1.1) | 2.13 (0.32) | 2.26 (0.34) | Active vs waitlist: Observed difference -5, effect size -0.48 (-0.97, -0.04), p=0.02 |

# Clinical evidence: Neupulse patient reported outcomes

| Study | Time point | Neupulse, mean (SD) | Sham stimulation, Mean (SD) | Waitlist, mean (SD) |
|---|---|---|---|---|
| Maiquez 2023 (Neupulse) | Baseline | 54.9 (24.6) | 52.8 (22.4) | 56.7 (24.1) |
| | 3 months | 46.7 (25.2) | 40.3 (23.6) | 52.1 (24.0) |
| Difference within group at time point | | t=2.64, p<0.015<br>(baseline vs 3 months) | t=3.9, p<0.0005<br>(baseline vs 3 months) | t=1.6, p=0.13<br>(baseline vs 4 weeks) |



C&A-GTS-QOL, child and adolescent Gilles de la Tourette quality of life scale

# Clinical evidence: intermediate outcomes (1)

| Intermediate outcomes | Hollis 2021 (ORBIT UK) | Andren 2022 (ORBIT Sweden) | Maiquez 2023 (Neupulse) |
|---|---|---|---|
| Adverse events (AE) | • 78.6% of the intervention group and 84.8% of the comparator group experienced an adverse event<br>• Unclear if they were related to the relevant intervention | 44 treatment-related AEs were reported | NR |
| Treatment satisfaction/engagement | • In the intervention arm, the median number of logins by the young person was 19 as compared to 9 in the comparator group.<br>• The median score for the young person's perception of treatment suitability and credibility was 7 in the intervention group and 6 in the comparator group.<br>• Mean child satisfaction scores with the ORBIT intervention were 24.8 out of 32 | • Both children and parents were more satisfied with the ORBIT intervention than the comparator treatment<br>• The treatment credibility score was identical for children and parents | NR |

# Clinical evidence: intermediate outcomes (2)

| Intermediate outcomes | Hollis 2021 (ORBIT UK) | Andren 2022 (ORBIT Sweden) | Maiquez 2023 (Neupulse) |
|---|---|---|---|
| Intervention adherence | NR | NR | • Measured by the iiPAS<br>• No differences between the groups |
| Rates and reasons for attrition | • Intervention group: 20.5% of participants were lost to follow-up at 18 months<br>• Comparator group: 19.6% were lost to follow-up at 18 months | • Intervention group: 3 were lost to follow-up at 3 months<br>• Comparator group: 2 were lost to follow-up at 3 months | 10 withdrawals during the initial training as the participants found the stimulation uncomfortable or insufficient time to complete the study or could not commit to participation. |
| Intervention completion (completion of at least the first four child chapters) | • Intervention group: 88.4%<br>• Comparator group: 93.8% | • Intervention group: 100%<br>• Comparator group: 94.6% | NR |



iiPAS: a 5-item, clinician-rated internet intervention Patient Adherence Scale

# Key uncertainty in clinical evidence (1)

The main limitation of the systematic review of clinical effectiveness was the paucity of evidence for the technologies of interest, including the limited amount of evidence, inconsistencies in the outcomes measured and the timing of these measurements.

The identified studies did not involve a comparison with face-to-face behavioural therapy, which is the current standard of care. Therefore, for the ORBIT studies, it was not possible to separate the effects of online delivery from those of ERP.

Both ORBIT studies did not include a non-active control treatment (e.g. waitlist) to evaluate the natural course of the disease over time, especially in young children.

Unclear why only the YGTSS-TTSS score was selected as the primary outcome in the included studies but not the YGTSS-Impairment score.

# Key uncertainty in clinical evidence (2)

Doubt on whether a reduction in tic severity translates into an improvement in daily life including self-esteem, social interactions and school/work performance because no improvements observed in the YGTSS-Impairment score and the inconsistent improvements in quality-of-life measures over follow-up times and across studies.

Both ORBIT studies included participants with moderate to severe tic disorders, who had a low rate of common comorbidities and modest use of medications for tics. Therefore, the reported findings cannot be generalisable to more severe tic disorder populations.

Most participants in at least one of the ORBIT studies (the UK study) were White, which limits the generalisation of findings to other ethnic groups

# Issues for consideration: clinical evidence

Does the evidence suggest a potential benefit for the use of digitally enabled technologies for the treatment of tic disorders and Tourette syndrome?

Does the evidence suggest the use of digitally enabled technologies is better than standard care as currently implemented in clinical practice for the treatment of chronic tic disorders?

There is limited evidence for sub-groups of children and young people with diagnosed comorbidities, including: attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), autism spectrum disorder (ASD), mood disorders, and anxiety.

Are any potential risks of using the digitally enabled technologies mitigated or minimised?

# Summary of published economic evidence

The model structure was based on the model developed alongside the recently published randomised controlled trial (RCT) by Hollis et al., which compared online ERP with online psychoeducation for tics in children.

| Study | Population | Country | Setting | Intervention | Comparator | DM type / health states | Time horizon |
|---|---|---|---|---|---|---|---|
| Hollis 2023 | Moderate / severe tic disorder (TS or CTD); mean age 12, 79%M | UK | CAMHS | Online therapist supported ERP | Online, therapist supported, psychoeducation | Type: Markov cohort model. States: Very mild, mild, moderate, severe, very severe | Trial: 18 M DM: 10 yrs. |

**EAG interpretation of relevance against NICE reference case and scope for this assessment:**
High. Detailed assessment of relevant intervention and includes a decision analysis model with an appropriate model structure parameterised using trial data from a UK NHS perspective. (Note that the comparator may not necessarily reflect UK clinical practice.)

**Assessment against Phillips criteria for decision modelling studies:**
Moderate. Well conducted study, with appropriate parameterisation using clinical data. Further scenario analyses and discussion around long-term extrapolation assumptions and intervention costing would have been helpful.

# Economic model overview

A Markov cohort model was constructed to assess the expected costs and QALYs of different treatments for managing tics and Tourette's syndrome in children and young adults.

Model outputs are used to calculate the expected net monetary benefit (NMB) for each strategy at a range of cost-effectiveness thresholds.

Two separate comparisons of cost-effectiveness:

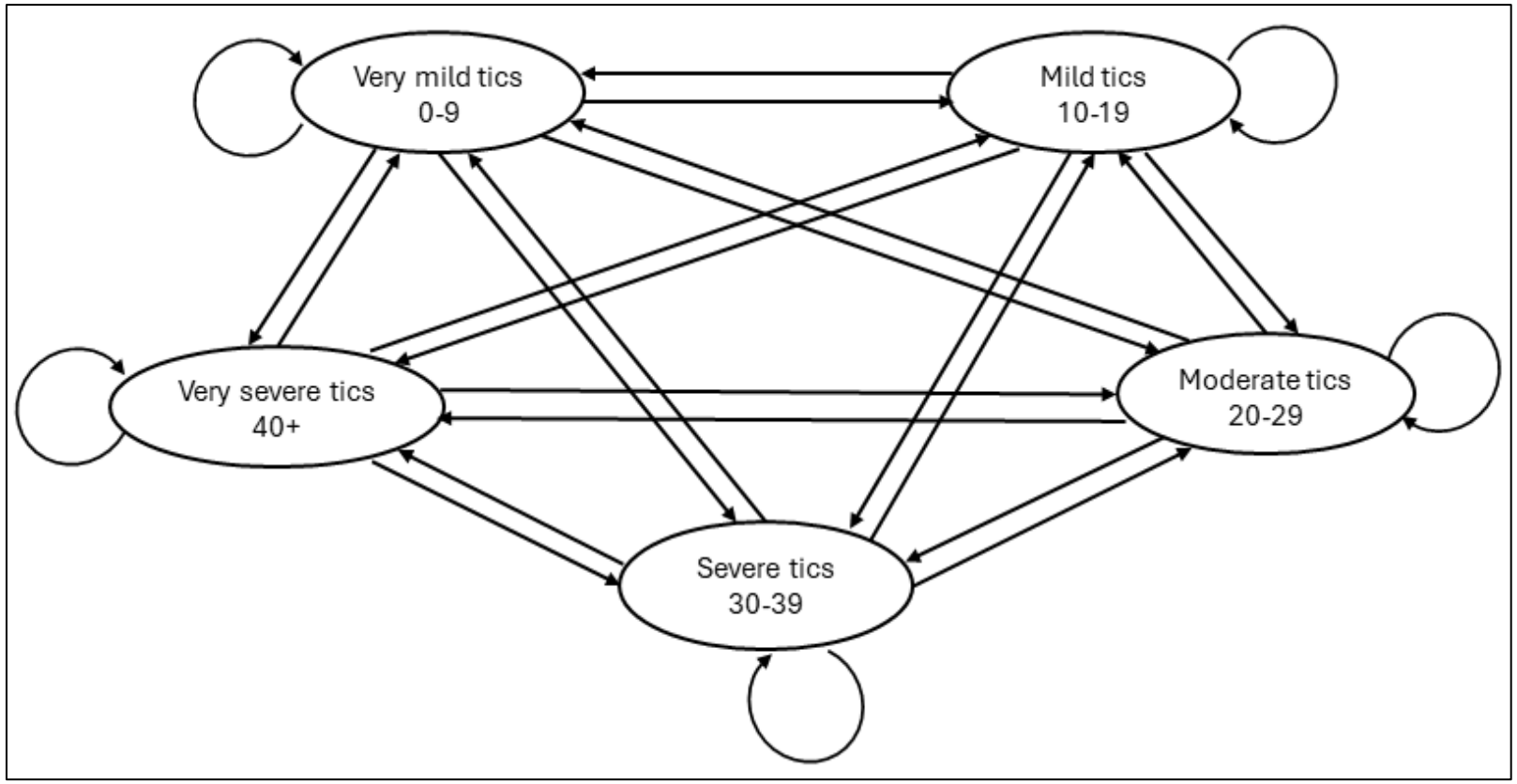
1) Online exposure and response prevention (ERP) therapy compared to online psychoeducation in children and adolescents
2) Neupulse stimulation compared to a waitlist control (i.e. no stimulation) in young adults



QALYs: Quality Adjusted Life Years RCT: randomised controlled trial ERP: exposure and response prevention

# Economic model structure

The model comprises five mutually exclusive health states that describe the severity of tics and TS, defined as quintiles of the YGTSS-TGSS score: very mild (0-9), mild (10-19), moderate (20-29), severe (30-39), and very severe (40-50).






YGTSS-TTSS, Yale Global Tic Severity Scale Total Tic Severity Score

# Economic model assumptions (1)

- The mean age of patients in the ORBIT trial was 12 years (14 at the end of the trial follow up). A lifetime time horizon of 88 years (86 years post-trial) is appropriate to capture all costs and outcomes.
- The comparators differ to the NICE scope, which stated face-to-face psychoeducation. However, the EAG were unable to find any evidence comparing the interventions to face-to-face psychoeducation and definitions of psychoeducation across other studies were too heterogeneous to enable any form of indirect comparison to be performed.
- Two different cycle lengths are considered: a 6-month cycle length for ORBIT and a 4-week cycle length for Neupulse. Cycle-lengths were chosen given the limited availability of data, especially for Neupulse.

# Economic model assumptions (2)

- The cohort can die from any state during the model according to all cause age and sex adjusted mortality probabilities. There is no excess mortality associated with tics and Tourette's syndrome included in the model.
- The model starting point is 18 months, as the model includes the costs and QALY payoffs reported in the clinical trial up to 18 months follow-up. A 2-year time horizon therefore refers to 18 months plus 2 years of extrapolation for the ORBIT comparison.  No cost-effectiveness trial data are available for the Neupulse; therefore, the model is started at time zero.

# Key evidence gap in the economic model (1)

- The long-term potential for people with chronic tic disorders or TS to become tic-free over time, into adulthood is unclear.  Scenario analyses explore the potential for this based on one small study, but caution is required regarding heterogeneity in the study.
- General point around limitations of published data and reliance on data provided directly from the company.  Results should be interpreted cautiously.
- The fully incremental analysis point is more about the heterogeneity in the underlying study populations.  Neupulse targeted towards older, perhaps at a different point in the care pathway. ORBIT and Neupulse therefore cannot be sensibly compared against each other for cost-effectiveness.

# Key evidence gap in the economic model (2)

- There was no evidence to enable a cost-effectiveness assessment of any of the interventions compared to current UK standard of care. The online psychoeducation arm of ORBIT uses the BiP platform and may therefore be a more active comparator than current UK clinical practice.
- A key uncertainty relates to long-term extrapolations beyond 18 months for the ORBIT comparison and beyond 4 weeks for the Neupulse comparison. It may therefore be appropriate to consider shorter time horizons given the lack of robust long-term data on tic / TS progression with and without treatment.

# Model parameters – transition probabilities

| Transition probabilities based on observed data | Key evidence gap |
|---|---|
| All transition probabilities are incorporated into the model using Dirichlet distributions using alpha values reflecting transition counts back calculated from transition probabilities reported in the ORBIT NIHR report. For Neupulse, the Dirichlet distributions are parameterised using 4 weekly alpha counts provided through personal communication with the company. | Neupulse transition probabilities were not available from the published literature and were instead sourced through personal communication with the company. Informing long-term projections on only 4-weeks of data is a key evidence gap. Transition probabilities for all comparisons (ORBIT and Neupulse), are derived from very small counts. This leads to substantial uncertainty regarding treatment effect sizes in the longer-term. |
| **Transition probabilities to the absorbing 'tics free' state in scenario analyses** | **Key evidence gap** |
| The intention of 'tics free' state is to model a proportion of people who may 'grow out' of tics in the longer term, returning to a quality of life assumed equal to that of the general population. The proportion of the cohort entering this state in the scenario analysis is derived from a study reporting that, over one-third (37%) of a combined sample of across two studies of N=82 children with TS were completely tic-free. | The long-term trajectory towards a tic-free state, i.e. the potential for people to have completely resolved tics over time, into adulthood is not well understood. Simplistic scenario analysis assumes that transitions occur at the same rate from any state of the model. This assumption is likely to lack face validity, given that people become tics gradually over time. |

# Model parameters – transition probabilities

| Longer-term transition probabilities beyond the end of the observed period from trial data | Key evidence gap |
|---|---|
| For online psychoeducation and ORBIT, we assume that the transition probabilities between 6 and 18 months can be extrapolated over a lifetime horizon. These transitions exclude the initial improvement in both arms seen up to 6 months in the study. It assumes that both ERP and online psychoeducation are successful longer-term and that learned behaviours can be implemented indefinitely.<br><br>For Neupulse, it assumes that the intervention is effective only so long as it is used, but that it is used for the full modelled time horizon. For the base case analysis, it is assumed that transition probabilities from 4-weeks can be extrapolated longer-term. Scenario analysis explores an assumption that full effectiveness for Neupulse is achieved at 4-weeks. Treatment is assumed to continue, but no additional benefit beyond 4-weeks is assumed. | Long-term transition probabilities are unknown for all the interventions. It is unclear how transition probabilities for Neupulse would change beyond the study intervention phase (4-weeks). There is some suggestion that transition probabilities for online psychoeducation may be slightly favourable to psychoeducation longer term suggesting that gains in the ERP arm might not be sustained longer-term. However, all these data are highly uncertain.<br>It is more appropriate to consider the balance of uncertainty around model outcomes using probabilistic analyses, with the uncertainty captured through small counts informing the Dirichlet distributions of transitions. |

# Model parameters – costs & resource use (1)

**ORBIT and online psychoeducation intervention cost:** All cost items for ERP and online psychoeducation were sourced directly from the ORBIT trial. Costs were split into an 'upfront' initial cost plus and ongoing cycle-specific cost based on variable cost of platform usage.

| Cost per participant | Initial up-front costs | | Ongoing costs per cycle | |
|---|---|---|---|---|
| | Psychoeducation | ERP | Psychoeducation | ERP |
| Fixed cost of BIP platform per participant | £43.05 | £43.05 | £0 | £0 |
| Fixed cost of Therapist support (training and supervision) | £75.38 | £75.38 | £0 | £0 |
| Annual variable platform costs | £6.32 | £7.73 | £6.32 | £7.73 |
| Variable cost of therapist support | £42.76 | £48.38 | £0 | £0 |
| Total intervention cost | £167.51 | £174.54 | £6.32 | £7.73 |

Evidence gap:

- It is unclear how the availability of the BiP platform would have impacted on the effectiveness of the online psychoeducation arm of the study, but it is plausible that it would have over-estimated effectiveness in the comparator arm relative to standard care where the platform was not available.
- Similarly, the exact throughput for the BiP platform is unclear, and this impacts on costs.
- It is unclear which combination of intervention costs and long-term extrapolations is most appropriate.

# Model parameters – costs & resource use (2)

**Neupulse intervention cost:** The cost for Neupulse consists of two components: an initial cost for purchasing the device with a usable life of [redacted] and a monthly subscription cost.

The monthly subscription includes access to an app for controlling the device, daily disposable hydrogel pads, storage of medical data associated with the therapy, and access to both digital and human product support resources.

| Cost item | Fixed |
|---|---|
| Neupulse device cost, incurred every [redacted] | [redacted] |
| Subscription cost/month | [redacted] |

Evidence gap:

- It is unclear how the costs provided would translate to costs in UK NHS practice if the device was made available to the NHS. However, it is feasible that a combination of factors, including additional costs of sales to the NHS, or reductions due to economies of scale would be relevant, meaning that the cost to the NHS may not be accurately represented by the costs used in the economic modelling.
- Whilst the company suggest that there are no training or staff costs associated with use of the device, there are, as yet no data to support or refute this assumption.

# Model parameters – costs & resource use (3)

Health state costs:

| Parameters | | Mean | SE | Source |
|---|---|---|---|---|
| 6-month health state costs | | | | |
| Very mild | Base case | £145.14 | £17.11 | ORBIT |
| | Scenario | £145.14 | £17.11 | ORBIT |
| Mild | Base case | £145.14 | £17.11 | ORBIT |
| | Scenario | £145.14 | £17.11 | ORBIT |
| Mod. | Base case | £149.64 | £14.21 | ORBIT |
| | Scenario | £166.91 | £16.69 | ORBIT + assumption |
| Severe | Base case | £218.28 | £21.40 | ORBIT |
| | Scenario | £235.06 | £23.51 | ORBIT + assumption |
| Very severe | Base case | £218.28 | £21.40 | ORBIT |
| | Scenario | £235.06 | £23.51 | ORBIT + assumption |
| No tics | | £0 | N/A | Assumption |

Evidence gap:

- There is limited evidence external to the clinical trial with regards to the most appropriate health state costs to apply in the economic model.
- The EAG are also aware that many people may not have access to services specifically to treat their tics / TS and that in some cases, these services may be embedded within other services for other co-morbid conditions.
- There are no data from the ORBIT study regarding the health state costs to apply for adults.

# Model parameters– Health state utility values

Health state utility values were obtained from the ORBIT study. In the ORBIT study, utilities were calculated from responses to the CHU9D.

Evidence gap:

- The relationship between tic severity and HRQoL is unclear. Changes in the clinical outcome do not necessarily lead to changes in quality of life or health state utility values.
- Whilst some evidence is available from the ORBIT study for children, there are no studies reporting the relationship between tic severity and EQ-5D in adult patients.
- It is unclear if the lack of statistical significance of health state in the ORBIT study is due to small sample sizes, or a true lack of effect.
- The lack of evidence is particularly acute in an adult population.

| Parameters | Mild | Moderate | Severe | No tics* |
|---|---|---|---|---|
| Mean | 0.867 | 0.839 | 0.814 | 0.867 |

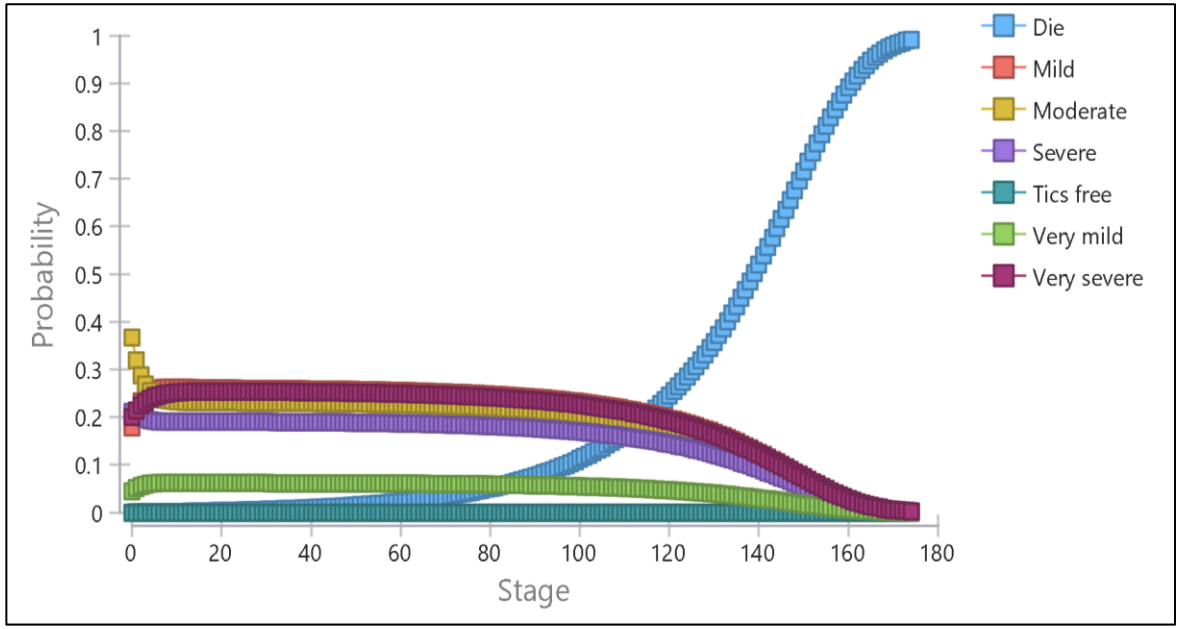


CHU9D: Child Health Utility 9D HRQoL: Health-related quality of life

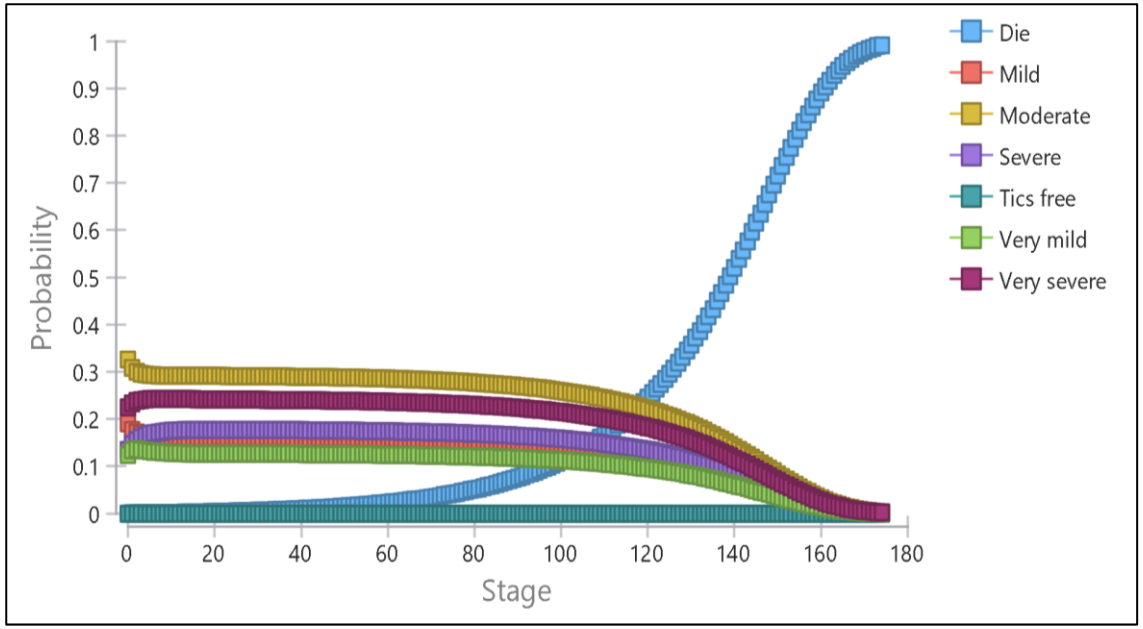
* This is an assumption that EAG imposed (equal to mild), rather than reported data from any studies.

# Base case results – ORBIT (1)

The cohort traces are very similar, particularly after the first few model cycles.  This is due to differences up to 18 months being quite quickly offset by slightly favourable, but highly uncertain transition probabilities for online psychoeducation.

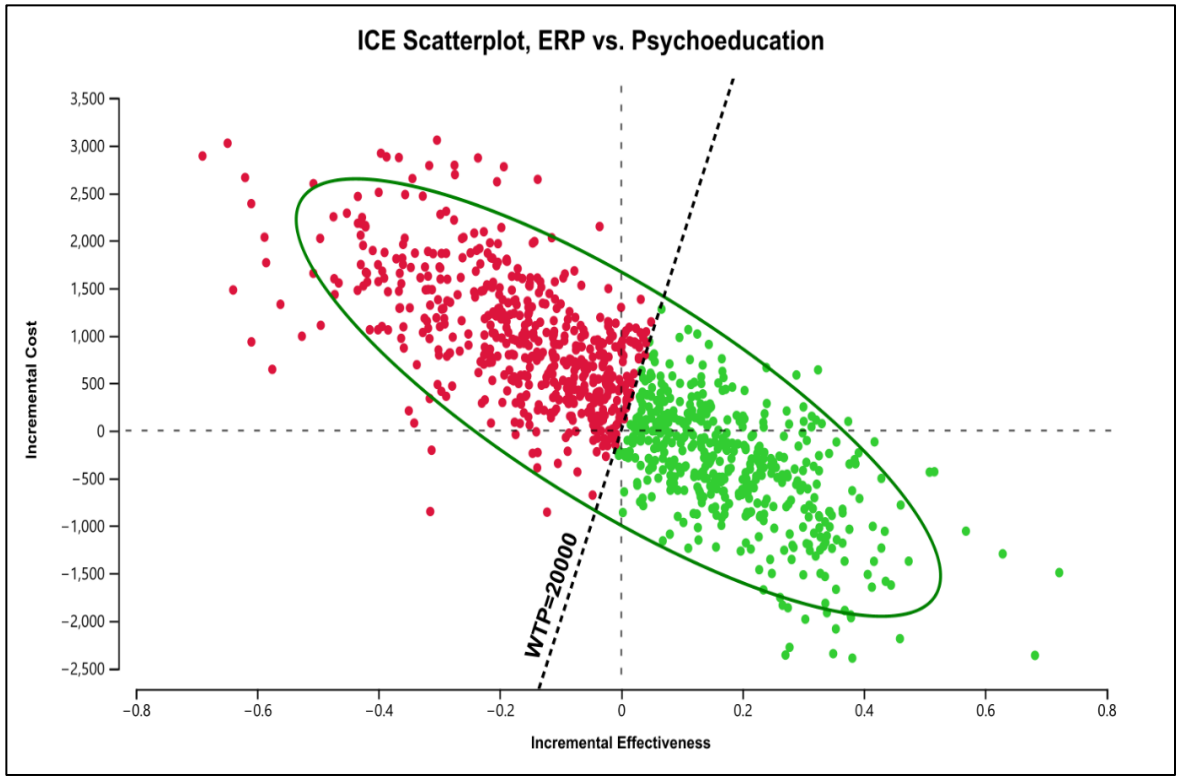



Markov cohort trace – online psychoeducation

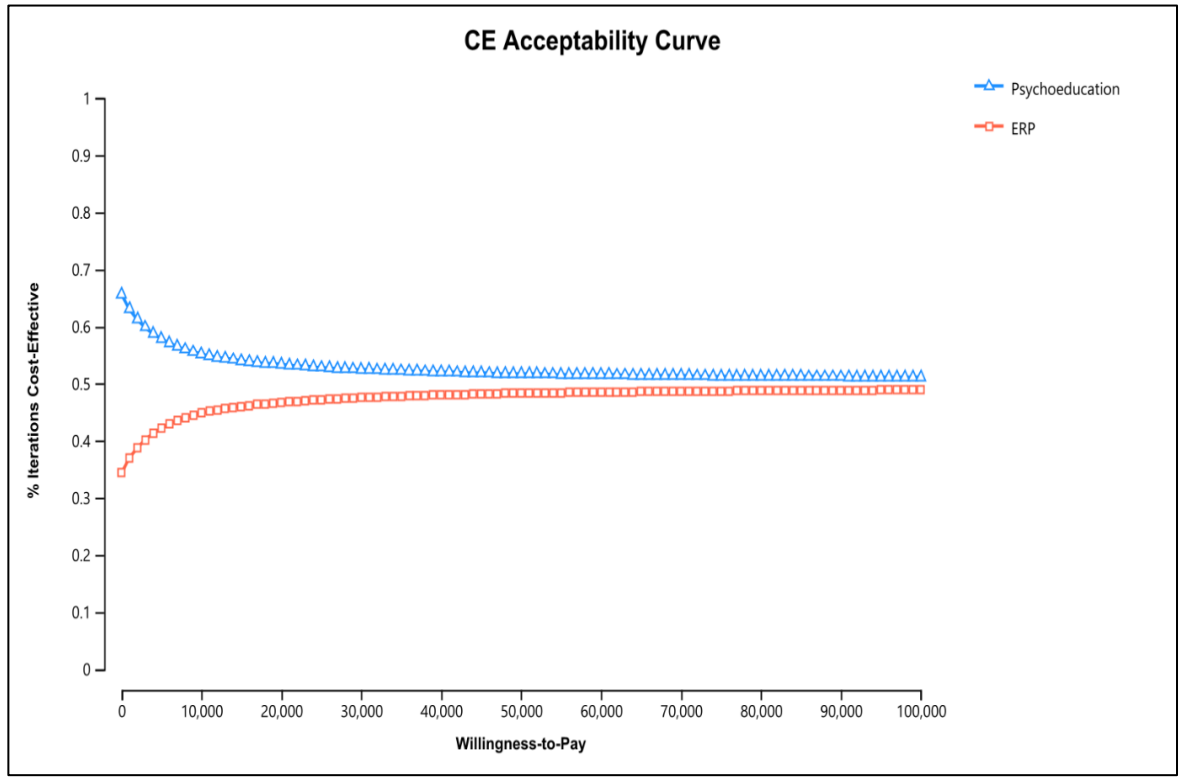



Markov cohort trace – ORBIT

# Base case results – ORBIT (2)




Base case incremental scatter plot of simulations on the cost-effectiveness plane for ORBIT vs. online psychoeducation




Base case cost-effectiveness acceptability curves for ORBIT and online psychoeducation.

# Base case results – ORBIT (3)

- Whilst these results may appear significantly different to each other, they should be interpreted in the context of the uncertainty surrounding the results output.
- Observation of the spread of iterations from the 50,000 iterations from the probabilistic analysis on the cost-effectiveness plane indicate substantial uncertainty.
- An approximately equal proportion of iterations lie above and below the £20,000 per QALY threshold line, indicating that neither strategy is clearly optimal under base case assumptions.
- Many of the simulated cost and effect pairs lie in the northwest quadrant of the plane, indicating that we cannot rule out ERP being more costly and less effective over a lifetime horizon.
- Cost-effectiveness acceptability curves also illustrate that the uncertainty persists across all threshold values of willingness to pay for a QALY gain.



Base case incremental scatter plot of simulations on the cost-effectiveness plane for ORBIT vs. online psychoeducation

# Base case results –ORBIT (4)

The deterministic analysis suggests a low ICER of £9,289 for ORBIT compared to online psychoeducation, whereas the probabilistic ICER shows ORBIT to be, on average, more costly with minimal differences in effectiveness (i.e. dominated by online psychoeducation).

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) |
|---|---|---|---|---|---|
| **Deterministic ICER** | | | | | |
| Psychoeducation | £12,755 | 20.916 | - | - | - |
| ERP | £12,974 | 20.939 | £218 | 0.024 | £9,289 |
| **Probabilistic ICER** | | | | | |
| Psychoeducation | £12,731 | 20.928 | - | - | - |
| ERP | £13,085 | 20.921 | £354 | -0.007 | Dominated |



QALY: quality adjusted life years ICER: incremental cost-effectiveness ratio ERP: Exposure, and response prevention

# Scenario analyses – ORBIT (1)

Further explore uncertainty surrounding key modelling assumptions, including intervention costing, long-term extrapolation of transition probabilities and the potential for inclusion of a tics free semi-absorbing state in the model.

In general results were most sensitive to assumptions about the costs of psychoeducation, including whether the variable costs of the platform are included.

The probability of ORBIT being cost-effective at a willingness to pay threshold of £20,000 per QALY gained varies between 45% up to 90% in a highly optimistic scenario where it is assumed that the cohort remain in their last observed health state at the end of the trial follow-up period.

# Scenario analyses – ORBIT (2)

| S. No | Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) |
|---|---|---|---|---|---|---|
| 0 | Base case | | | | | |
| | Psychoeducation | £12,731 | 20.928 | - | - | - |
| | ERP | £13,085 | 20.921 | £354 | -0.007 | Dominated |
| 1 | Time horizon = 10 years from end of trial follow-up (18 months + 10 years) | | | | | |
| | Psychoeducation | £5,123 | 7.741 | - | - | - |
| | ERP | £5,417 | 7.763 | £294 | 0.023 | £12,867 |
| 2 | Times horizon = 5 years from end of trial follow-up (18 months + 5 years) | | | | | |
| | Psychoeducation | £3,422 | 4.593 | - | - | - |
| | ERP | £3,707 | 4.622 | £285 | 0.029 | £9,936 |
| 3 | Time horizon = 2 years from end of trial follow-up (18 months + 2 years) | | | | | |
| | Psychoeducation | £2,253 | 2.413 | - | - | - |
| | ERP | £2,541 | 2.443 | £289 | 0.030 | £9,611 |

# Scenario analyses – ORBIT (3)

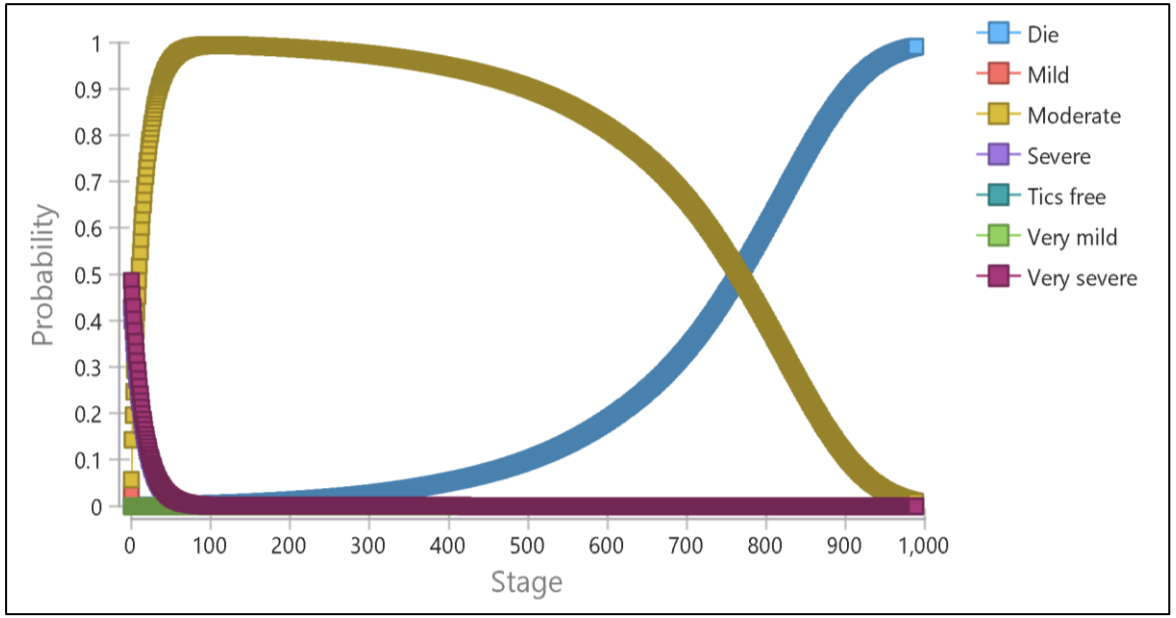
| S. No | Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) |
|---|---|---|---|---|---|---|
| 4 | Include transitions into the absorbing 'tics free' health state, set utility tics free = mild | | | | | |
| | Psychoeducation | £5,947 | 21.311 | - | - | - |
| | ERP | £6,254 | 21.324 | £306 | 0.013 | £22,979 |
| 5 | Include only variable cost of therapist support for psychoeducation | | | | | |
| | Psychoeducation | £12,495 | 20.928 | - | - | |
| | ERP | £13,088 | 20.921 | £593 | -0.007 | Dominated |
| 6 | Apply approach from ORBIT study (include only variable platform costs and therapist support for psychoeducation; remove all ongoing costs) | | | | | |
| | Psychoeducation | £12,489 | 20.928 | - | - | |
| | ERP | £12,936 | 20.922 | £447 | -0.006 | Dominated |
| 7 | Only include variable therapist support costs, include ongoing costs + platform throughput (n=100) | | | | | |
| | Psychoeducation | £12,615 | 20.927 | - | - | - |
| | ERP | £13,145 | 20.920 | £530 | -0.007 | Dominated |
| 8 | Only include variable therapist support costs, include ongoing costs + platform throughput (n=1000) | | | | | |
| | Psychoeducation | £12,603 | 20.928 | - | - | - |
| | ERP | £13,054 | 20.920 | £451 | -0.008 | Dominated |

# Scenario analyses – ORBIT (4)

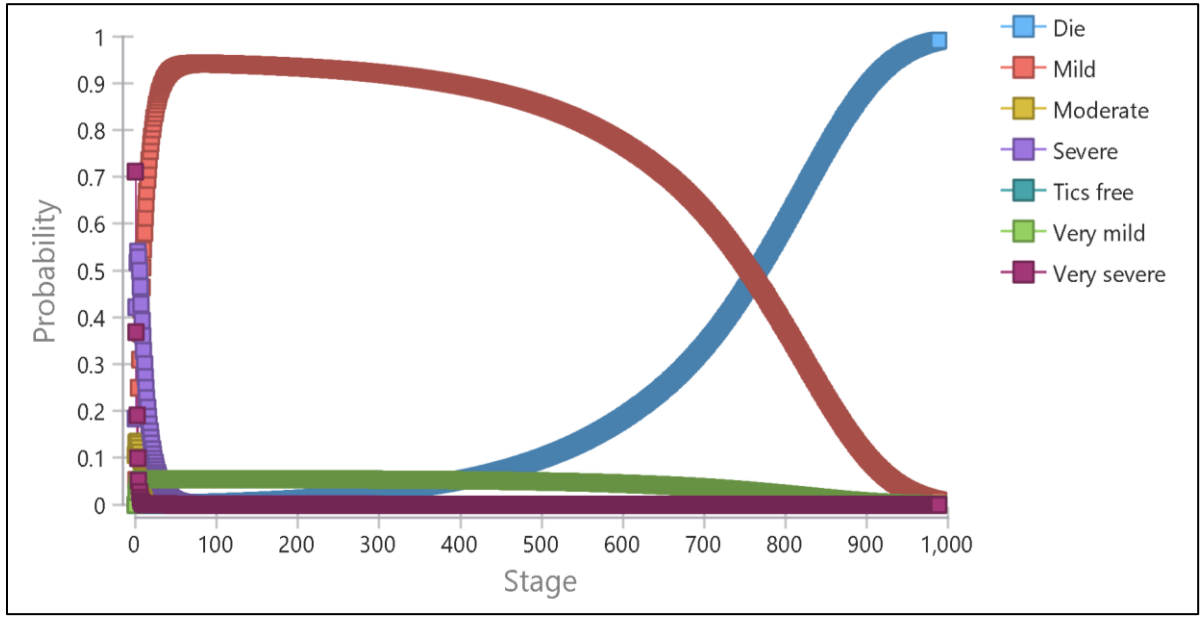
| S. No | Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) |
|---|---|---|---|---|---|---|
| 9 | Remove ongoing costs from both arms | | | | | |
| | Psychoeducation | £12,619 | 20.928 | - | - | - |
| | ERP | £12,946 | 20.922 | £327 | -0.006 | Dominated |
| 10 | Remove long-term transition probabilities (retain in state beyond 18 months), assumes 18-month benefit retained indefinitely | | | | | |
| | Psychoeducation | £12,647 | 20.871 | - | - | - |
| | ERP | £12,723 | 20.989 | £76 | 0.119 | £642 |
| 11 | ERP transition probabilities revert to online psychoeducation arm after 18 months | | | | | |
| | Psychoeducation | £12,730 | 20.928 | - | - | - |
| | ERP | £13,010 | 20.962 | £281 | 0.033 | £8,419 |
| 12 | Apply additional medication costs to moderate and severe health states | | | | | |
| | Psychoeducation | £13,416 | 20.929 | - | - | - |
| | ERP | £13,830 | 20.921 | £415 | -0.008 | Dominated |

# Base case results – Neupulse (1)

The Markov cohort traces show a clear difference between the Neupulse arm, with most of the cohort in the mild health state over time, compared to the waiting list control arm, with the majority in the moderate health state.




Base case Markov cohort traces for wait list control




Base case Markov cohort traces for Neupulse

# Base case results – Neupulse (2)

Due to the lack of available data to populate the Neupulse model, it is not reasonable to derive a definitive base case analysis.

Neupulse is almost [redacted] as costly as the waiting list control at the prices provided by the company. The additional costs are driven by [redacted] device replacement and the [redacted], which would be the minimum costs required to allow extrapolation of highly optimistic 4-weekly transition probabilities over a lifetime horizon.

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) |
|---|---|---|---|---|---|
| Deterministic ICER | | | | | |
| Waiting list control | £7,693 | 19.138 | - | - | - |
| Neupulse | [redacted] | 19.765 | [redacted] | 0.627 | [redacted] |
| Probabilistic ICER | | | | | |
| Waiting list control | £7,796 | 19.118 | - | - | - |
| Neupulse | [redacted] | 19.690 | [redacted] | 0.572 | [redacted] |

# Base case results – Neupulse (2)

Incremental scatter plot of simulations on the cost-effectiveness plane for Neupulse vs. wait list control

Cost-effectiveness acceptability curves for Neupulse and wait list control

# Scenario analyses – Neupulse (1)

Results were most sensitive to assumptions about the long-term extrapolation from 4-weeks onwards, clearly demonstrating the need for future research around long-term effectiveness.

Different assumptions cause wide variation in the ICER between just over £10,000 per QALY gained in an optimistic scenario analysis that extrapolates 4-weekly transitions for a lifetime (probability of cost-effective = 87%) to over £300,000 per QALY in the less optimistic scenario analysis (probability cost-effective = 0%) where transitions are crossed over to the waitlist control group after the observed 4-week period.

# Scenario analyses – Neupulse (2)

| S. No | Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) |
|---|---|---|---|---|---|---|
| 0 | Base case | | | | | |
| | Wait list control | £7,796 | 19.118 | - | - | - |
| | Neupulse | [redacted] | 19.690 | [redacted] | 0.572 | [redacted] |
| 1 | Time horizon = 10 years | | | | | |
| | Wait list control | £2,830 | 6.924 | | | |
| | Neupulse | [redacted] | 7.110 | [redacted] | 0.186 | [redacted] |
| 2 | Time horizon = 5 years | | | | | |
| | Wait list control | £1,600 | 3.742 | | | |
| | Neupulse | [redacted] | 3.835 | [redacted] | 0.092 | [redacted] |
| 3 | Time horizon = 2 years | | | | | |
| | Wait list control | £710 | 1.535 | | | |
| | Neupulse | [redacted] | 1.566 | [redacted] | 0.031 | [redacted] |

# Scenario analyses – Neupulse (3)

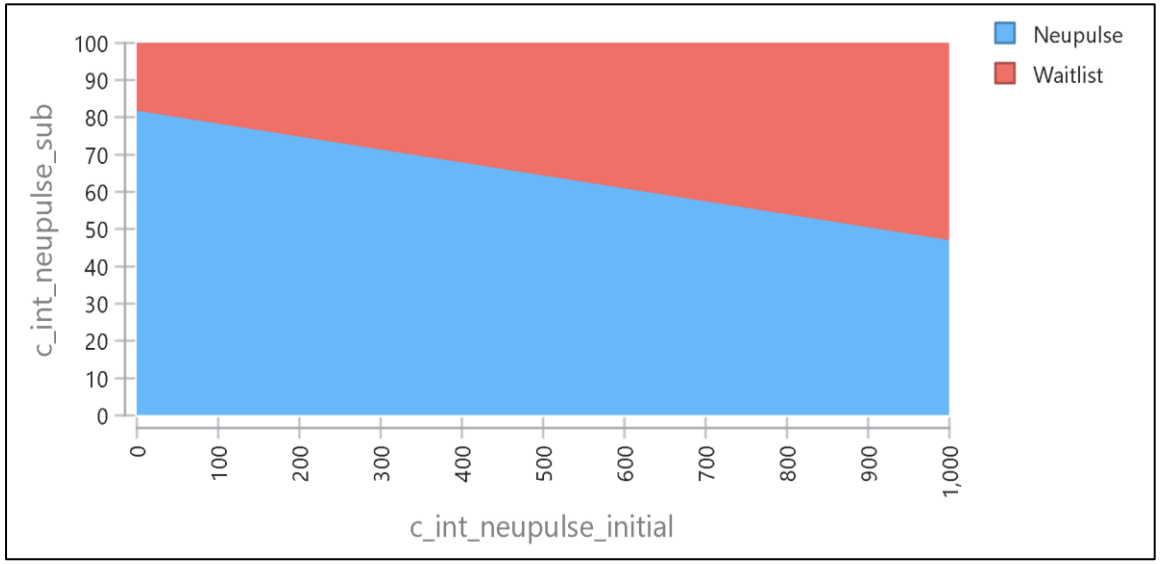
| S. No | Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) |
|---|---|---|---|---|---|---|
| 4 | Include transitions into the absorbing 'tics free' health state, set utility tics free = mild | | | | | |
| | Wait list control | £3,330 | 19.475 | - | - | - |
| | Neupulse | [redacted] | 19.721 | [redacted] | 0.247 | [redacted] |
| 5 | Long-term transition probabilities: set equal to zero, assumes no further improvement of regression of tics and TS after 4 weeks | | | | | |
| | Wait list control | £10,703 | 18.659 | - | - | - |
| | Neupulse | [redacted] | 18.763 | [redacted] | 0.104 | [redacted] |
| 6 | Long-term transition probabilities: assume that Neupulse cohort reverts to 'no treatment' transition matrix after 4 weeks | | | | | |
| | Wait list control | £7,802 | 19.119 | - | - | - |
| | Neupulse | [redacted] | 19.141 | [redacted] | 0.022 | [redacted] |
| 7 | Apply additional medication costs to moderate and severe health states | | | | | |
| | Wait list control | £8,675 | 19.119 | - | - | - |
| | Neupulse | [redacted] | 19.690 | [redacted] | 0.572 | [redacted] |

# Scenario analyses – Neupulse (4)

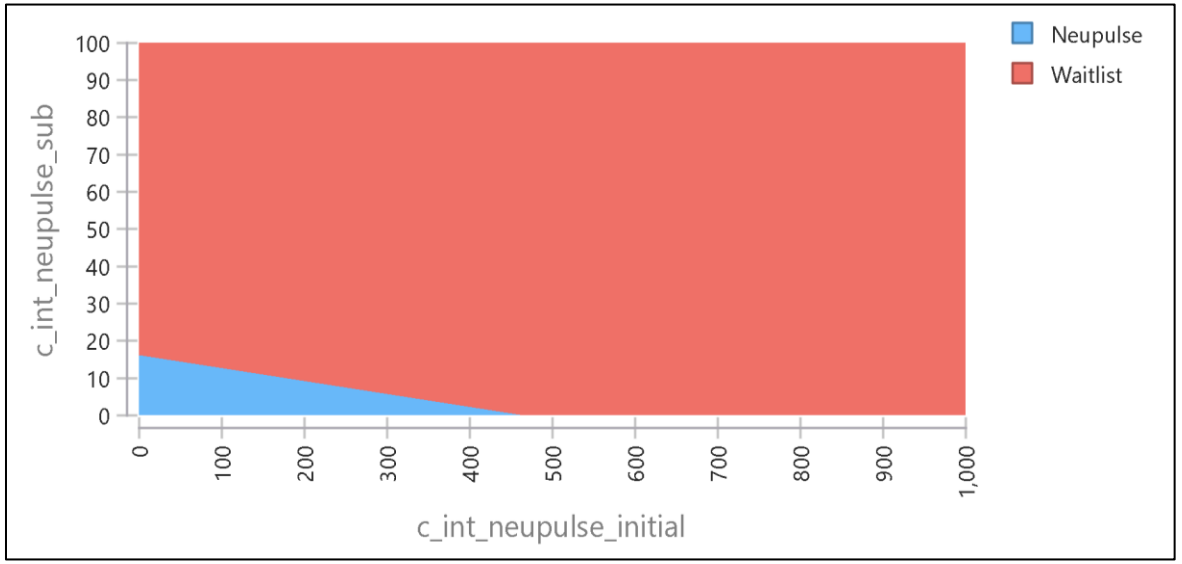
Due to the confidential nature of initial and ongoing Neupulse intervention costs, two-way scenario analyses are conducted.

These scenarios are applied to long-term transition probabilities (4-weekly transitions are carried forward, and the cohort fixed in state after 4 weeks, assuming maximum effectiveness achieved at 4 weeks). Analyses are based on NMBs with a WTP = £20,000 per QALY.

Results of these analyses further emphasise the substantial residual uncertainty.




Two-way scenario analysis of initial and subscription costs for Neupulse (assumes long-term transition probabilities extrapolated)




Two-way scenario analysis of initial and subscription costs for Neupulse (assumes cohort held in last observed state)

# Key uncertainty in economic evidence

Economic modelling shows that there remains substantial residual uncertainty in the assessment of cost-effectiveness for both interventions.  Key areas of remaining uncertainty include:

1) non-publicly available Neupulse pricing information
2) short follow-up of only 4-weeks for Neupulse
3) Unclear long-term intervention costs that would be required to deliver trial observed benefits
4) Uncertainty about the most appropriate link between tic severity score and health state costs and utilities, in particular whether small improvements in YGTSS scores have a direct impact on generic quality of life measures such as EQ-5D or CHU-9D
5) A lack of information about long-term effectiveness beyond the trial follow up periods to inform economic modelling

Scenario and probabilistic sensitivity analyses show that there is substantial residual uncertainty, making it difficult to define the most plausible ICERs for either comparison.

# Issues for consideration: economic evidence

The results from the economic modelling of ORBIT should be interpreted considering the uncertainty surrounding the model outputs. ORBIT may be cost-effective compared to standard care in the case with the deterministic point estimate of the ICER, but given the longer-term uncertainty, base case assumptions that ORBIT is not (or is unlikely to be) cost-effective from the distribution of Base case incremental scatter plot.

High uncertainty in the cost-effectiveness results of Neupulse due to lack of evidence.

The assessment of cost-effectiveness relied on several major, but highly uncertain assumptions about longer term intervention costs that might be required to maintain the intervention's effectiveness as well as the most appropriate long-term extrapolation assumptions.

# Key areas for future research

Future replication is needed to confirm the observed results in the included studies.

Future studies of longer duration should compare digitally enabled therapy for tics versus face-to-face behavioural therapy and should also consider including a non-active intervention (e.g., waitlist) to monitor the natural course of the disease over time.

Future studies should measure the impact of digitally enabled therapy on participants’ daily lives as their primary outcome.

Appropriate subgroup analyses  are needed according to the participants' sex distribution (males versus females) and common comorbidities.

Future studies should include economic evaluations and should consider collection of longitudinal data to improve long-term modelling of treatment effectiveness.

NICE National Institute for Health and Care Excellence

# Thank you

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# Possible recommendations

## Conditionally recommended for use while further evidence is generated

- Likely that the technology will solve the unmet need and it is acceptable for the technology to be used in practice while further evidence is generated

## Recommended only in a research context

- Uncertain if the technology has the potential to solve the unmet need, or it is not acceptable to be widely used in practice while further evidence is generated

## Not recommended for use

- Unlikely that a technology has the potential to meet the unmet need, or where there are concerns about the potential harms associated with using the technology even in a research context

# National Institute for Health and Care Excellence

# Health technologies evaluation programme

## Digitally enabled therapy for chronic tic disorders and Tourette Syndrome: External Assessment Report Collated Table

| # | Commenter name | Group | E-mail address | Date received |
|---|---|---|---|---|
| 1 | Tara Murphy | **SCM** | | 05.08.24 |
| 2 | Tourettes Action | **Patient organization** | | 05.08.24 |
| 3 | ORBIT study team University of Nottingham | **NIHR MindTech HealthTech Research Centre** | | 05.08.24 |
| 4 | Jeremy Stern | **SCM** | | 05.08.24 |
| 5 | Stacey Chang-Douglass | **SCM** | | 05.08.24 |

| Comment no. | Commentator | Page | Section | Comments | EAG Response |
|---|---|---|---|---|---|
| 1 | Tara Murphy Great Ormond Street Hospital NHS Trust | Strengths, limitations and uncertainties | xvii | The reason(s) for selection of only the YGTSS-TTSS score as the primary outcome in the included studies, rather than the YGTSS-Impairment score, is unclear.<br><br>Haas et al highlight the differences in the measurement from the YGTSS vs the TTSS. I read this to mean that the Impairment subscale can 'drown out' the scores from the TTSS, due to the different anchor points in the measures. It is common practice to use the TTSS in intervention trials of tic disorder and this should not be seen as a limitation to the | Thank you for raising this point. We accept that the YGTSS-TTSS score is commonly used in research of this population. However, we note that the impairment score may reflect the actual effect on patients' daily lives and social interactions – in other words, a reduction in tic severity may not |



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| | | | | | |
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| | | | | studies reported on the EAR. Generally, what is considered to be effective tic interventions result in about 25% reduction on the TTSS.<br><br>https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2021.626459/full<br><br>Wen et al (2021) examined the psychometric properties of the YGTSS. The researchers found that the functional impairment content was not well-defined, potentially leading to confusion among raters, and suggested that a revised version of the YGTSS should include more detailed impairment items with more appropriate weighting (https://bmcpsychiatry.biomedcentral.com/articles/10.1186/s12888-021-03399-5)<br><br>The YGTSS is a recommended tic instrument and considered the most reliable and widely research outcome tool in research in tic disorders. This has been shown in several studies such as: Storch, Eric A.,Murphy, Tanya K.,Geffken, Gary R.,Sajid, Muhammad,Allen, Pam,Roberti, Jonathan W.,Goodman, Wayne K. Psychological Assessment, Vol 17(4), Dec 2005, 486-491; Jeon S, Walkup JT, Woods DW, Peterson A, Piacentini J, Wilhelm S, Katsovich L, McGuire JF, Dziura J, Scahill L. Detecting a clinically meaningful change in tic severity in Tourette syndrome: a comparison of three methods. Contemp Clin Trials. 2013 Nov;36(2):414-20. doi: 10.1016/j.cct.2013.08.012. Epub 2013 Aug 31. PMID: 24001701; PMCID: PMC3999642. | be translate in an improvement in day-to-day life, which is, in fact, what our findings suggest.<br><br>The paper by Haas et al. (https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2021.626459/fu) while recognising that the YGTSS has an acceptable psychometric quality, suggest the need for further investigations and improvements of the scale. In addition, their results show limitations of the global severity score as a sum score indicating that the separate use of the total tic score and the impairment rating is more beneficial. The ORBIT trials have reported the severity score and the impairment score separately and our analyses and interpretation reflect this. Please note that the Wen et al. study is restricted to a small Chinese population. |
| 2 | Tara Murphy Great Ormond | Abstract | xi | Both ORBIT and Neupulse appear to significantly reduce YGTSS-TTSS scores but there were no improvements in the YGTSS-Impairment scores and mixed results across other secondary outcomes, meaning it is unclear to what extent | Thank you for your comment. The statement was based on the findings of our review which showed that tic severity scores |



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| | | | | | |
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| | Street Hospital NHS Trust | | | improvements in tic severity scores can translate to improvements in quality of life<br><br>There is a body of evidence showing that tic severity scores correlate with quality of life. Quality of life and daily function is notoriously difficult to assess particularly with the waxing and waning of tics over time.<br><br>Isaacs, Riordan & Claassen et al (2021)<br>Greater tic severity correlated with poorer physical HRQOL, measured by the GTS-QoL<br>www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2021.619854/full#B13<br><br>Evans, Stefano & Cavanna (2016)<br>Systematic review that describes tic severity on QOL. The challenges of having severe tics, particularly those causing pain or physical damage, significantly correlates with quality of life. https://link.springer.com/article/10.1007/s00787-016-0823-8 | decreased but that quality-of-life scores and other measures assessed during the studies did not show a reliable pattern of improvement. We accept that other research may show an association between tic severity and quality of life, but our comment relates to the effectiveness findings of our review. Moreover, it is always challenging to demonstrate how the magnitude of change in a scale score translates into QALY benefits. |
| 3 | Tara Murphy Great Ormond Street Hospital NHS Trust | Key areas for future research | xvii | Future studies should be of longer duration and compare the clinical and cost effectiveness of digitally enabled with face-to-face behavioural therapy<br><br>While this is desirable, 18 months for the ORBIT trial is to date the longest follow up period in this field. The only other study with a longer follow up period was follow up of 10 years, (Espil et al, 2021; J Am Acad Child Adolesc Psychiatry) and the attrition level was so high the data were barely interpretable. | Thank you. We understand that studies of longer duration may be problematic to conduct. |
| 4 | Tara Murphy | Current manage ment and | 2 | The NICE Guideline 127 on 'Suspected Neurological Conditions: Recognition and Referral' contains some information on tic disorders | Thank you for pointing this out. |



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| | | | | | |
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| | Great Ormond Street Hospital NHS Trust | clinical pathway | | A significant limitation of this guidance is that it does not include the first line intervention for all professionals which is to give patients, families etc basic psychoeducation about tics. This is clearly stated across all existing guidance available to date. | |
| 5 | Tara Murphy Great Ormond Street Hospital NHS Trust | Aim and Objectives | 10 | Small note here that the revised version of ORBIT will refer to Therapists as eCoaches. This modification follows results from participants in the process evaluation assessment (reference below) from the ORBIT trial that the 'Therapist role' is not therapy-based but more akin to coaching to enhance motivation and support operational use of the ORBIT platform.<br><br>Khan K, Hollis C, Hall CL, Davies EB, Mataix-Cols D, Andrén P, Murphy T, Brown BJ, Murray E, Glazebrook C. Protocol for the Process Evaluation of the Online Remote Behavioural Intervention for Tics (ORBIT) randomized controlled trial for children and young people. Trials. 2020 Jan 2;21(1):6. doi: 10.1186/s13063-019-3974-3. PMID: 31898510; PMCID: PMC6941346. | Thank you for the clarification. |
| 6 | Tara Murphy Great Ormond Street Hospital NHS Trust | *Characteristics of included studies* | 16 | Evidence gap: Evidence was not available to compare the interventions under investigation and face-to-face behavioural therapy, the current standard of care.<br><br>• It might be helpful to mention that although pre-COVID pandemic face to face behavioural therapy might have been standard care this is not the case in post-pandemic care in which many NHS Trust now use remote treatment more consistently and have the appropriate procedures in place to do so. Many services deliver remote behavioural therapy individual | Thank you for this information. We appreciate that face-to-face therapy may no longer be considered current standard of care, although standard care may vary between centres. Please note that the NICE final scope specified face-to-face behavioural therapy as the main relevant comparator. |



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| | | | | treatment, or remote group based behavioural therapy. There are few high standard studies supporting this modality of delivery, but it is the current practice. This is similar to the model developed in the United States, as practitioners delivering treatment are few and patients are not able to travel to appointments without disrupting working and educational lives. Future research will need to consider what standard care actually is. The INTEND study which is currently being carried out by Dr Maddie Groom at Uni of Nottingham has demonstrated some alarming results to date and a study carried out a decade ago (Cuenca et al, 2015 (DOI: 10.1186/s12888-015-0430-0) also showed poor and inconsistent care / treatment for children and young people with TS across England, which was delivered well below expectation.<br><br>**Relevant publications:**<br>Himle MB, Freitag M, Walther M, Franklin SA, Ely L, Woods DW, et al. randomized pilot trial comparing videoconference versus face-to-face delivery of behavior therapy for childhood tic disorders. Behav Res Ther. (2012) 50:565– 70. doi: 10.1016/j.brat.2012.05.009 13.<br><br>Himle MB, Olufs E, Himle J, Tucker BTP, Woods DW. Behavior therapy for tics via videoconference delivery: an initial pilot test in children. Cogn Behav Pract. (2010) 17:329–37. doi: 10.1016/j.cbpra.2010.02.006<br><br>Ricketts EJ, Goetz AR, Capriotti MR, Bauer CC, Brei NG, Himle MB, et al. A randomized waitlist-controlled pilot trial of voice over Internet protocol-delivered behavior therapy for | |


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| | | | | youth with chronic tic disorders. J Telemed Telecare. (2016) 22:153–62. doi: 10.1177/1357633X15593192 | |
| 7 | Tara Murphy Great Ormond Street Hospital NHS Trust | *Characteristics of included studies* | 17 | *Uncertainty: It was unclear whether the participants in the two ORBIT trials had access to psychoeducation prior to recruitment into the trials. Access to psychoeducation was not an inclusion criterion for either trial.*<br><br>While this is correct, ORBIT/BIPTIC include a module focused entirely on psychoeducational material ( in both the child and supporter intervention for both ERP & psychoeducation) and additional information added in the subsequent chapters:<br><br>1. **Learn about tics/introduction (reported in page 8 of EAR)**<br><br>Module 1 covers all of the commonly required material in recommended psychoeducational material. Participants could review it as often as they desired. | Thank you for this information. |
| 8 | Tara Murphy Great Ormond Street Hospital NHS Trust | Economic model overview | 43 | The specific objectives are: To evaluate the safety and effectiveness of digitally enabled non-pharmacological therapy for treating chronic tic disorders and Tourette Syndrome in UK clinical practice;<br><br>The EAR notes that “It should however be noted that the online psychoeducation comparator does not align directly with the NICE scope”<br><br>While this is true, most psychoeducational material is accessed by patients through books, webinars, podcasts, YouTube videos etc rather than face to face psychoeducation. Psychoeducation can be considered to be a first line intervention and universal for all sufferers of tic disorders | Thanks for this clarification. Please note that this review was conducted in line with the NICE final scope. |



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| 9 | Tara Murphy Great Ormond Street Hospital NHS Trust | **Economic model overview**<br><br>***Transition probabilities to the absorbing 'tics free' state in scenario analyses*** | 45 55 | The EAR states: An option for an absorbing state of "no tics" is included to explore the impact on results of an assumption that some people may gain complete control of tics and Tourette's syndrome over time, into adulthood, without treatment.<br><br>This statement is not fully accurate. It's not that people with TS gain complete control over tics, it is more accurate to say that the tics no longer occur. It is likely that very few individuals every fully grow out of their tics, although for most they do reduce with time ( Groth C, Mol Debes N, Rask CU, Lange T, Skov L. Course of Tourette Syndrome and Comorbidities in a Large Prospective Clinical Study. J Am Acad Child Adolesc Psychiatry. 2017 Apr;56(4):304-312. doi: 10.1016/j.jaac.2017.01.010. Epub 2017 Feb 2. PMID: 28335874.) | Thank you for the clarification. In our economic model, our base case analysis assumes that tics do not fully resolve over time and may continue to occur. The long-term probability of this in the economic model is derived from the transition probabilities in the ORBIT and Neupulse studies (extrapolated from the reported data over the longer term). To account for a proportion of people in whom tics no longer occur, we conducted a scenario analysis to explore the impact of this on cost-effectiveness results. |
| 10 | Tara Murphy Great Ormond Street Hospital NHS Trust | **Model parameters - health state utility values (HSUVs)** | 62 | It should be noted that many patients with TS move between severity states of tics, due to the natural waxing and waning of tics.<br><br>This is less true for the co-occurring conditions that most people with TS suffer, which are more stable over years, although may remit or reduce in adulthood. Interesting recent German paper describing the differences across development here (MOVEMENT DISORDERS CLINICAL PRACTICE 2024. doi: 10.1002/mdc3.14167) | Thank you for the additional resource. Given the data available, we were not able to account directly for co-occurring conditions in our health state utility values, though the modelled values will reflect the quality of life associated with the distribution of co-occurring conditions observed in the ORBIT study. |
| 11 | Tara Murphy Great Ormond Street | **Model parameters - health state** | 63 | *Evidence gaps: As demonstrated in the clinical-effectiveness review, the relationship between*<br>*tic severity and HRQoL is unclear. Changes in the clinical outcome do not necessarily lead* | Thank you. We can clarify that our point here relates to the health state utility values included in the economic model, where it was difficult to |



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| | Hospital NHS Trust | **utility values (HSUVs)** | | *to changes in quality of life or health state utility values. This is an important area for future research. Whilst some evidence is available from the ORBIT study for children, there are no studies reporting the relationship between tic severity and EQ-5D in adult patients. The EAG understands the rationale for pooling very mild / mild and very severe / severe states for*64 *calculating HSUVs. However, if a true relationship between tic severity and generic HRQoL exists, the approach may underestimate the QALY benefits of effective treatments. It is unclear if the lack of statistical significance of health state in the ORBIT study is due to small sample sizes, or a true lack of effect. Further studies are required to better understand the relationship between tic severity and QALY benefits. The lack of evidence is particularly acute in an adult population.*<br><br>*There are studies of QoL and tic severity and other co-occurring factors in adults with TS, such as (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7987653/pdf/fpsyt-12-619854.pdf)* | determine with any accuracy the impact on CHU-9D utilities of a one-unit change in YGTSS-TTSS. It was also unclear what magnitude of effect size on YGTSS would translate into QALY gains. However, the correlation between QoL (CHU-9D) and YGTSS-TTSS score is indirectly captured in the economic model with higher utility values assigned to less severe (lower score) YGTSS-TTSS states. |
| 12 | Tara Murphy Great Ormond Street Hospital NHS Trust | **Model validation and face validity checks** | 65 | However, they did flag that the highly uncertain evidence base meant that caution should be exercised when interpreting the results of a lifetime horizon model, given the lack of longer term follow up beyond 18 months for ORBIT and lack of published transition probability data for Neupulse.<br><br>I think it's important to appraise this consideration in light of the existing evidence-base in tic disorder, as mentioned | Thank you for this comment. Given the substantial longer-term uncertainty, there may be an argument in this case for considering a time horizon in the economic model that is shorter than a lifetime. Extrapolating short-term trends (e.g. between 12 and 18 months) for ORBIT |



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| | | | | above. Few neurodevelopmental conditions (including tics) have post-intervention outcome data beyond 12 / 18 months. It will be helpful to be realistic about what evidence will be available in the UK in the future and how long it may take to collect more data while evidence-based interventions remain scarcely available in the NHS. | and online psychoeducation into the longer term may lead to overall QALY outcomes that are biased in favour of online psychoeducation. We have therefore provided scenario analyses that extrapolate over 2, 5 and 10 years. Shorter time horizons might not capture the full magnitude of long-term costs and benefits related to a treatment decision, but the outcomes are likely to be less biased by long-term extrapolation assumptions. |
| 13 | Tara Murphy Great Ormond Street Hospital NHS Trust | **Model validation and face validity checks** | 66 | Obtained from the ORBIT study, includes only the costs of using specialist tic services<br><br>Treatment costs are similar across the UK whether patients are given the same treatment within a specialist centre or community specialist service. | Thank you for this clarification. |
| 14 | Tara Murphy Great Ormond Street Hospital NHS Trust | **Strengths and limitations of the assessment and uncertainties** | 85 | The identified studies did not involve a comparison with face-to-face behavioural therapy, which is the current standard of care.<br><br>This is not currently true, much treatment is delivered remotely and within groups in current practice. | We appreciate that standard care practices can differ between centres, including remote and group-based delivery methods. However, without additional data, it is premature to conclude that standard care is predominantly delivered online or in groups. Notably, face-to-face therapy was identified as the primary |



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| | | | | | comparator in the NICE final scope. Furthermore, considering that the BIP platform was utilised in the online psychoeducation group, the control group in the ORBIT study might represent a more active form of care compared to what is typically offered in routine NHS practice. |
| 15 | Tara Murphy Great Ormond Street Hospital NHS Trust | **Strengths and limitations of the assessment and uncertainties** | 85 | Moreover, both ORBIT studies did not include a non-active control treatment (e.g. waitlist) to evaluate the natural course of the disease over time, especially in young children.<br><br>The youngest child recruited to the ORBIT trial was 9 years of age, this would not be considered to be a 'young child' as tics typically onset 4-7 years of age and there is an evidence base for (face to face) behavioural therapy for children as young as 5 years of age (Bennett, Shannon M.; Capriotti, Matthew R.; Bauer, Christopher C.; Chang, Susanna W.; Keller, Alex E.; Walkup, John T.; Woods, Douglas W.; and Piacentini, John, "Development and Open Trial of a Psychosocial Intervention for Young Children with Chronic Tics: The CBIT-JR Study" (2020). Psychology Faculty Research and Publications. 510.) Many well designed studies in TS do not include a non-active control treatment arm. | Thank you for your comment. |
| 16 | Tara Murphy Great Ormond Street Hospital NHS Trust | **Strengths and limitations of the assessment and** | 85 | It is also unclear why only the YGTSS-TTSS score was selected as the primary outcome in the included studies but not the YGTSS-Impairment score.<br><br>It is recommended that the authors revise the literature of primary outcome measures in TS, before accepting this | If the YGTSS Impairment subscale is rarely used in research, its inclusion as a secondary outcome measure by the trial investigators of all included studies raises questions. |



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| | | **uncertainties** | | conclusion as the Impairment subscale in the YGTSS is rarely used in research. | |
| 17 | Tara Murphy Great Ormond Street Hospital NHS Trust | **Strengths and limitations of the assessment and uncertainties** | 85 | Similarly, most participants in at least one of the ORBIT studies (the UK study) were White, which limits the generalisation of findings to other ethnic groups.<br><br>While this is true, and indeed a pity, it reflects patient cohorts in UK NHS clinics, it was reported in this specialist clinic and will be reported in a more detailed future paper based on these data which is currently about to be submitted but is not currently available in the public domain. https://cdn.prod.website-files.com/5df74fd26a31d55fb945366c/666321cc381f04f43cf514bf_12%20Archer%20%26%20Shoaib%20(Parikh).pdf and the situation is similar in USA clinics: https://www.neurology.org/doi/10.1212/WNL.0000000000202214 | Thank you for your comment. |
| 18 | Tara Murphy Great Ormond Street Hospital NHS Trust | **Key areas for future research** | 86 | Future studies of longer duration should compare digitally enabled therapy for tics versus face-to-face behavioural therapy and should also consider including a non-active intervention (e.g., waitlist) to monitor the natural course of the disease over time.<br><br>While I agree that the above statement applies to Neupulse (which requires no individual therapeutic input), and I look forward to hearing about data from a longer following up period, I don't think that we can hope for funding for further ORBIT trials with longer follow up periods with comparison to 1:1 face to face treatment. We do not have enough trained therapists or in the UK to enable this. The CBITs trial which evaluated HRT vs Psychoeducation in the 2000s in the US (child study - Piacentini et al, 2010; adult study - Wilhelm et al, 2012) had very high costs and was carried out across 5 | Thank you for this information. |



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| | | | | centres and it only had half the sample size of the ORBIT trials. | |
| 19 | Tara Murphy Great Ormond Street Hospital NHS Trust | **Key areas for future research** | 86 | In addition to tic severity, future studies should measure the impact of digitally enabled therapy on participants' daily lives as their primary outcome.<br><br>This is an interesting recommendation, and it would be helpful to hear suggestions of how the authors would see this impact being operationalised with specific examples, as the measures used in both the ORBIT and Neupulse studies are considered to be 'gold standard' and those most frequently used in tic disorder research. | Thank you. The suggestion here is to use quality of life or activities of daily living as primary outcomes. |
| 20 | **Tourettes Action** | Background | 11 | Background states "Digitally enabled interventions may help improve patient outcomes." I think it would be better to state that "Access to treatment is limited and sporadic throughout the country, access to digitally enabled interventions would allow more people to access treatment, which may help improve patient outcomes." | Thank you for your suggestion. |
| 21 | **Tourettes Action** | Scientific Summary background | 13 | It states "and then improving through adolescence into early adulthood." This isn't always the case, tics can improve in some cases but not all. Some are reported to 'grow out' of tics but it is unclear how many people this is true for and also whether the tics reappear at some points in the future. | Thank you for the clarification. |
| 22 | **Tourettes Action** | Scientific Summary background | 13 | It states 'People with chronic tic disorders commonly experience psychiatric comorbidities such' should however say 'People with tic disorders commonly experience psychiatric comorbidities such' as this affects both people with Tourette's and people with Chronic tic disorders. | Thank you for drawing our attention to this. |



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| 23 | **Tourettes Action** | Scientific Summary background | 13 | Again this sentence should say tic disorder and not chronic tic disorder ‘but, in general, treatment options for chronic tic disorders include psychoeducation, behavioural therapy, pharmacological therapy, and deep brain stimulation.’ | Thank you for the clarification. |
| 24 | **Tourettes Action** | Current management and clinical management | 21 | It states ‘As tics may improve with time, the NICE Guideline 127 indicates that for individuals presenting in primary care a watch-and-wait approach is considered acceptable, especially for those who do not experience any functional impairment.’<br><br>Not sure a watch and wait approach is acceptable, as yes tics may improve over time but if someone presents to primary care, who have had tics for over 1 year, they should be referred on for a diagnosis, as the tics may not improve for many years, if at all. Watch and wait is only a useful approach if the tics have been present for less than 12 months. | Thank you. As noted, this is the recommendation of NICE Guideline 127. |
| 25 | **Tourettes Action** | Current management and clinical management | 20 | This section states ‘Current practice varies between countries and according to the availability of local services but, in general, treatment options for chronic tic disorders include psychoeducation, behavioural therapy, pharmacological therapy, and deep brain stimulation.’ | No response is needed. There does not seem to be a comment attached to the quotation. |
| 26 | **Tourettes Action** | General statement | | The scientific summary background defines what chronic tic disorder and Tourette syndrome as ‘Persistent or chronic tic disorders refer to single or multiple motor or vocal tics (but not both) that have persisted for more than 12 months since the first tic onset. Tourette syndrome refers to multiple motor tics and one or more vocal tics that have been present at the same time (but not necessarily concurrently) during the course of the disease and have persisted for more than 12 months since the first tic onset.‘ but then in many sections Chronic tic disorder seems to be used as an overarching label | Thank you for your suggestion. |



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| | | | | to include both chronic tic disorder and Tourette syndrome. It would read better if either both labels were used or tic disorder was used to define both | |
| 27 | **Tourettes Action** | Population and relevant sub groups | 23 | It states:<br>Where data permit, the following subgroups were considered:<br>• Children and young people with diagnosed comorbidities, including attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), autism spectrum disorder (ASD), mood disorders, and anxiety.<br>• Adults with chronic tic disorders.<br><br>This appears that the only people who were considered where those who either had a comorbidity or adults. If this is the case, then why are children who do not have a diagnosed comorbidity not being considered? These children currently fall through the gaps as many clinicians will not see children with tics alone. Often, CAMHS will see if they have cooccurring anxiety, neurodevelopmental services will see if they have cooccurring ADHD, if they only have Tourette syndrome, they are often left in limbo unable to access a service. Just because an individual doesn't have a cooccurring conditions, doesn't mean it is less bothersome and they will almost always have traits of other conditions, even if they do not hit the threshold for a diagnosis.<br><br>I assume these children have also been included but I think the wording possibly makes it appear that they haven't been included. | Thank you. These are pre-specified subgroups, which indicates the groups would be looked at in more detail within the study population, if data were available. |
| 28 | ORBIT study team University of | General | | It is our view that the External Assessment Report (EAR) has misspecified the decision problem. The Final Protocol stated that the research question was 'Are non-pharmacological interventions delivered remotely/online better than standard | We thank the ORBIT study team for their comments. For the economic model, it was our initial plan to consider current |



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| | Nottingham, NIHR MindTech HealthTech Research Centre | | | care as currently implemented in clinical practice?' Rather than considering the **potential** clinical and cost-effectiveness of **clinical pathways** including ORBIT compared to standard of care clinical pathway, the assessment has simply adopted the decision problem investigated by the ORBIT trial. This means that the comparison made in the health economic analysis is between psychoeducation and exposure and response prevention (ERP) therapy using ORBIT, both delivered predominantly digitally. Although it was appropriate to design our clinical trial with an active comparator (psychoeducation), in reality current standard of care does not offer this consistently. We feel it would have been more appropriate to compare a potential pathway including ORBIT to a standard of care pathway where, as the EAR notes, as many as 80% of young people are not able to access face to face therapy and in many areas people with tic disorders are referred across multiple services unable to receive any treatment at all. We feel that the current report could make a more balanced assessment of the clinical and potential cost effectiveness of ORBIT. It could be noted from existing evidence that both psychoeducation and ORBIT delivered digitally are clinically effective. The costs and consequences could also be presented separately rather than as ICERs so that a lay reader could see that both psychoeducation and ORBIT deliver improvements in symptoms and in quality of life for a relatively low cost.<br><br>As part of our current NIHR funded project, we will undertake a health economic analysis (including a budget impact analysis) which will compare a number of feasible clinical pathways, using a stepped-care approach, incorporating psychoeducation, ORBIT and face to face therapy with current heterogenous standard of care. We recognise that | clinical management. However, given that current standard of care is heterogeneous across the UK, it was not possible to model this pathway with any degree of accuracy. We also do not have good quality longitudinal data that would allow an accurate assessment of tic severity, quality of life, or costs in the current pathway.<br>We do agree that there is a need for further studies to address this question.<br>We acknowledge that work is ongoing in this area and thank the ORBIT study team for the information provided. We believe any additional evidence that can be provided around care pathway costs will be helpful for future modelling work.<br>Whilst very helpful, the additional cost data provided still does not address the key concern around long-term extrapolation of effectiveness data. |



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| | | | | there are many areas of uncertainty around current pathways and the costs of these, but we do know that patients currently use non-trivial healthcare system resources in trying to have their needs addressed (see appendix). We aim to reduce these uncertainties through our current funded research programme and would ask the EAR to provide a more considered recommendation which takes our current research programme into account. We have provided responses to particular comments made using the current decision scope but would prefer that the decision problem should be revisited in line with the EAR report section 3.3.2 which states that the model would be parameterised reflecting current standard of care in UK clinical practice rather than 'gold standard care pathway' if this was required. | |
| 29 | ORBIT study team University of Nottingham, NIHR MindTech HealthTech Research Centre | Abstract - methods | xi | The decision problem does not reflect current UK practice with lack of access to evidence-based behavioural therapy for tic disorders. Although the Background section acknowledges service availability this is not considered in the decision problem. In our view, the population of interest is **all** patients with confirmed primary chronic tic disorder (as stated in Table 2 of the EAR). This may be as part of a stepped or blended care approach (see Key Areas for Future Research P93 of HTA report (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10641713). The intervention would be a clinical pathway incorporating ORBIT in an appropriate position in that pathway. Comparator would be standard of care (SOC) clinical pathways including no provision for a large proportion of patients. Note that at present in the UK, pathways are sufficiently heterogenous that NIHR have funded the INTEND study [NIHR204897] to map current provision. There is a lack of provision for these patients in many areas with our team's earlier qualitative work | Thank you for this additional information. |



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| | | | | finding that patients are referred multiple times between agencies leading to long delays in them receiving any treatment and high costs for health systems with multiple wasted appointments.<br><br>We include, as an example, an appendix at the end of this table which cites two patient journeys of access to care – alongside associated costs. Personal information has been redacted and the names are pseudonyms. However, this data is currently under review for publication and is not for reporting in the public domain at present. The case studies detail the long delay and high usage/costs to other healthcare systems as a result of no/poor access to care. | |
| 30 | ORBIT study team University of Nottingham, NIHR MindTech HealthTech Research Centre | Abstract - methods | xi | We question the value of replicating an NIHR-funded HTA ORBIT trial decision model which was designed as an economic evaluation alongside a clinical trial and where the intervention and comparator were determined by the design of the RCT to demonstrate efficacy of online ERP rather than reflect current UK clinical practice (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10641713). Note that RCTs in this field are very difficult to compare due to different levels of tic severity, patterns of co-morbidity and different inclusion/exclusion criteria. | Thank you. We agree that current standard of care would be the ideal comparator, and it was our intention to model this, but due to a lack of consistency in clinical practice, and in particular a lack of longitudinal data on tic severity (and natural history) in the UK, it was not possible to accurately build such a model. In the absence of other evidence, we considered that replicating the ORBIT model and conducting wider scenario analyses would provide useful indications of the key drivers of cost-effectiveness that could be considered in future studies. We look forward to the results of the |



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| | | | | | health economic analyses of pathways, which are currently being developed by your team. |
| 31 | ORBIT study team University of Nottingham, NIHR MindTech HealthTech Research Centre | Abstract - results | xi | The phrase "*but there were mixed results for other secondary outcomes*" feels overly negative. The ORBIT trial was not powered for secondary outcomes. Hence, negative (statistical) findings for secondary outcomes should be treated with equal caution as positive ones. Furthermore, we wouldn't necessarily anticipate that a specific intervention designed to treat tics would improve low mood and anxiety, at least in the short term. Downstream impacts of tic reduction on wider social functioning, quality of life, mood and anxiety are likely to take time to accrue – hence, the importance in the UK ORBIT study of long-term follow-up to 18 months. For example, in the UK ORBIT study showed significant benefits only at longer-term follow-up for depression at 12 months (ES 0.26; 95% CI 0.51 to 0.01) and 18 months (ES 0.43; 95% CI 0.70 to 0.15); and for anxiety at 12 months (ES 0.31; 95% CI 0.53 to 0.08) and 18 months (ES 0.49; 95% CI 0.74 to 0.25). It would also be useful for the report to note where outcomes showed a point estimate which favoured ORBIT ERP even if they did not quite reach statistical significance. | Our systematic review considered all relevant outcome measures and was not restricted to the YGTSS-TTSS subscale We have provided an objective report of the variability in the direction of effects across the trials and outcomes. The outcomes from the three trials are available in our report for an objective and comprehensive overview of the three trials. |
| 32 | ORBIT study team University of Nottingham, NIHR MindTech HealthTech Research Centre | Abstract - General | xi/xii | We note the objective 'to evaluate the clinical and cost effectiveness' of ORBIT and the use of the phrase 'definitive base case ICER'. The evidence base for ORBIT is evolving. Would it be more appropriate to be considering the **potential** for ORBIT to be used in a position in the pathway which would improve health outcomes at an acceptable cost to the NHS? Given that the standard approach in the MTEP programme is cost minimisation, why is a cost-utility approach taken? Could cost consequence results also be provided to inform the reader? | We appreciate the comments and feedback. Our results tables include both mean modelled costs and QALYs for each intervention, and we have also provided incremental costs. We agree with the comment that there is very little difference in QALYs (or at least much uncertainty around the |



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| | | | | | magnitude of incremental QALYs), and so it may be appropriate to focus on costs. However, cost estimates over the longer term are also uncertain.<br><br>We believe that we have provided sufficient information for the committee to consider a cost-minimisation approach if deemed appropriate. |
| 33 | ORBIT study team University of Nottingham, NIHR MindTech HealthTech Research Centre | Abstract - results | xii | The sole focus on the ICER is not appropriate given the level of uncertainty in the model and the stage of development of the technology. It would perhaps be appropriate to include in the abstract the small differences in costs and QALYs between the two interventions compared in the trial. If ICERs must be quoted, it should be made clear how they can be highly variable when the QALY gain, or loss is small. | We completely agree with this statement. The magnitude of QALY differences is small and reliance on a single point estimate of the ICER would be misleading. Space in abstracts is very limited, but we can confirm that our view is that the spread of uncertainty on the cost-effectiveness plane should be the primary consideration for decision-making. |
| 34 | ORBIT study team University of Nottingham, NIHR MindTech HealthTech | Abstract - results | xii | It would be useful to mention the fact that both ORBIT and psychoeducation are relatively cheap interventions, and both were shown to be effective in the ORBIT trial. Providing ORBIT as the initial therapeutic intervention in a stepped care programme following (online) psychoeducation would allow many more patients to be treated and the very limited provision of existing trained therapists to see the most severely impacted patients face to face as ORBIT requires relatively little therapist input and those therapists do not need | It is our understanding that the stepped-care approach is a suggestion of the authors of the ORBIT study. As such, we do not believe it is our place to comment on a hypothetical pathway. |



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| | Research Centre | | | the same level of expertise as those delivering face to face ERP. Given the workforce capacity constraints and ongoing work to understand and standardise clinical pathways for patients with suspected tic disorders, it would be useful if the EAR could comment on ORBIT's potential role within a redesigned stepped-care pathway to meet current clinical needs in a cost-effective manner. It should also be stressed that currently most young people (regardless of severity) are unlikely to be able to access evidence-based behavioural therapy for their tics. | |
| 35 | ORBIT study team University of Nottingham, NIHR MindTech HealthTech Research Centre | General | No specific page | We would like to draw the committee's attention to our choice of comparator in the ORBIT trial. Psychoeducation was a stringent control group, offering an active intervention, over-and-above what most young people in England currently receive. We chose psychoeducation in line with previous research, including large-scale RCTs published in JAMA, who used psychoeducation as their control group. Thus, our research replicates and builds upon existing research in the field of tic therapy.<br><br>https://jamanetwork.com/journals/jama/article-abstract/185896<br><br>https://jamanetwork.com/journals/jamapsychiatry/article-abstract/1307556 | Thank you. Information about the interventions and comparators in the trials in available in our report. |
| 36 | ORBIT study team University of Nottingham, | Abstract - results | xii | Phrase "even more uncertain" feels overly negative – please rephrase. | This relates to the following statement:<br>*"Cost-effectiveness results for Neupulse were even more uncertain due to a lack of* |



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| | NIHR MindTech HealthTech Research Centre | | | | *published data, only 4-week follow up, and uncertainty surrounding the intervention cost."*<br>We believe this statement is justified. Results for the comparison of Neupulse compared to waiting list control were more uncertain than the results of the ORBIT. psychoeducation comparison. That is because there were no transition probabilities in the published literature and follow-up was only of 4-weeks duration for Neupulse. |
| 37 | ORBIT study team University of Nottingham, NIHR MindTech HealthTech Research Centre | Abstract - Limitations | xii | The sentence "*comparators did not include face to face therapy*" is incorrect for ORBIT. Although the trial did not include a face to face arm, the 10 year health economic model in the HTA report did include a face to face therapy arm: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10641713/ . Although, please note given the lack of capacity for face-to-face therapy, neither this nor psychoeducation, are consistently available to people with tic disorders in the UK. Thus, our comparator was more stringent than either "routine care" (i.e. absence of care) or waitlist comparator. Hence, the demonstrated efficacy of ORBIT and benefits for most secondary outcomes, particularly at longer term follow-up should be viewed in this light. | We intended to refer to the trial comparators in this statement. We fully acknowledge that CBIT was included in the economic model within the ORBIT study.<br><br>However, it is important to note that the inclusion of CBIT required a very strong assumption that transition probabilities beyond six months in the CBIT arm were equivalent to the ERP arm of the model. There does not appear to be a strong justification for this assumption. Indeed, this very limitation around a lack of data |



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| | | | | | was a key reason why we felt it was not appropriate to include a face-to-face comparator in our evaluation. Any effect sizes would be based on naïve comparisons across highly heterogeneous studies, without detailed reports of transition probabilities and the results of any such economic modelling would be highly speculative. |
| 38 | ORBIT study team University of Nottingham, NIHR MindTech HealthTech Research Centre | Abstract - Limitations | | The sentence "*cost effectiveness results should be interpreted cautiously due to lack of long-term evidence*" feels overly negative. ORBIT has clinical and cost effectiveness data up to18 months demonstrating durable benefits, which is longer than most trials of behavioural therapies and digital interventions. Follow-up studies of similar duration of behavioural (and digital) interventions are exceedingly rare and exceptionally difficult to fund. 18 months follow-up in the ORBIT trial is to date the longest follow up period in this field. The only other study with a longer follow up period was a naturalistic follow up 10 years post intervention, (Espil et al, 2021; J Am Acad Child Adolesc Psychiatry) and although the drop out level was very high, the active intervention using behavioural therapy outperformed the psychoeducation intervention. | We fully accept that the ORBIT study provides the best available evidence. Our point here was not intended as a criticism of the study but rather an acknowledgement that good quality longitudinal data are lacking. This inevitably translates into uncertainties around extrapolation modelling, as it is unknown to what extent treatment effectiveness is maintained indefinitely or if a treatment effect waning may occur over time. We provided several scenario analyses to explore this uncertainty in the EAR. |
| | | Abstract and general | xii | The sentence "*there were no improvements in the YGTSS impairment scores*" is potentially misleading as it refers only to statistical significance and places undue precedence on the YGTSS Impairment scale (which has weak psychometric | We conducted meta-analyses of YGTSS-Impairment scores at 3- and 12-months in the two ORBIT trials. The results |



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| | | | | properties) over other measures of global functioning and quality of life described in the NICE scope including CGI-I, C-GAS and C&A-GTS-QoL scale. The YGTSS Impairment scale is based on ratings of limited information in the YGTSS, and largely reflects the raters impression of impairment based on the YGTSS-TTSS score. The impairment subscale of the YGTSS is also limited to the preceding week whereas the other measures reflect a longer period.<br><br>First, it should be noted that despite serious limitations of the scale, YGTSS Impairment was reduced across both ERP and psychoeducation groups, with larger reductions in the ERP vs. psychoeducation group at 3 months (29.8% with EPR vs. 16.6% with psychoeducation) and 6 months (38.2% with ERP vs. 25.8% with psychoeducation). The effect size for ERP on YGSS Impairment score at 6 months was 0.24 (0.53 to -0.05). Although this is a meaningful point estimated difference, it should be noted that the trial was not statistically powered for secondary outcomes including the YGTSS Impairment score.<br><br>Second, online supported psychoeducation is an active comparator which would be expected to benefit overall functioning (rather than specific tic reduction), -particularly in the period when young people and families have access to this supportive intervention during the first 3 months of the trial. Psychoeducation is not currently available as a standard intervention for most people with tic disorders, which may well explain why impairment scores improved across both groups. We would expect comparison with a waitlist control to show larger differences. We believe having an active online comparator was a strength of the ORBIT trial in isolating the active component of the online ERP intervention. However, this design is also likely to have underestimated intervention | showed lower scores in the intervention than the comparator groups but not to the level of statistical significance. Thus, we consider that our statement is an objective report of our findings. Moreover, it is difficult to fathom why trial investigators of all included studies chose to include the YGTSS Impairment scale, despite its known weak psychometric properties. Additionally, the ORBIT published articles and HTA report fail to clearly disclose that the trial was underpowered for secondary outcomes. |



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| | | | | effects of online ERP compared to NHS routine care where neither ERP nor psychoeducation is typically available. We believe that there is a need for both psychoeducation and ERP in future clinical pathways, and that these findings demonstrate the potential of both interventions to be effective solutions in comparison to the current standard of care which routinely includes neither.<br><br>Third, other relevant secondary outcomes of overall functioning and quality of life included the Clinician Global Impressions – Improvement score (CGI-I), Children's Global Assessment Scale (C-GAS) and the Child and Adolescent Gilles de la Tourette Quality of Life (C&A GTS QoL) scale; Our long-term follow-up showed that online ERP had significant benefits on overall functioning and quality of life as measured by CGI-I at 12 months [ES 0.43; (95% CI 0.74 to0.21)] and 18 months [ES 0.35 (95% CI 0.66 to 0.04)]; GAS at 12 months [ES 0.22 (95% CI 0.43 to 0.01)] and 18 months [ES 0.25 (95%CI 0.46 to 0.04)]; and C&A-GTS-QoL at 12 months [ES 0.34 (95% CI 0.61 to 0.08)] and 18 months [ES 0.54 (95% CI 0.83 to 0.24)]. These long-term findings are important as they demonstrate the benefits of ORBIT for global functioning and quality of life that accrue over time from a short-term (12 week) skills-based ERP intervention.<br><br>We disagree with the EAR authors who suggest that the YGTSS Impairment score should be a primary outcome. As noted previously, the YGTSS Impairment score (0 to 50 scale) has been shown to have poorer psychometric properties (including larger standard deviation) than the other YGTSS subscales, thus, we do not consider it surprising that this may have not reached statistical significance. For example, Haas et al (2021) analysed the factor structure of | |



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| | | | | the YGTSS and found that loadings for the impairment score were low. This suggests the impairment score has limited factorial validity https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2021.626459/full. Additionally, Wen et al (2021) examined the psychometric properties of the YGTSS and found that the functional impairment content was not well-defined, potentially leading to confusion among raters https://bmcpsychiatry.biomedcentral.com/articles/10.1186/s12888-021-03399-5. Anecdotally, this aligns with clinical practice, whereby clinicians typically use the YGTSS-Total Tic Severity Score (TTSS) combined with a different measure of functional outcome such as the CGI-I, C-GAS and C&A-GTS-QoL scale as inter-rater reliability is significantly poorer for the YGTSS Impairment scale than the YGTSS TTSS.<br><br>The sentence “mixed results across other secondary outcomes, meaning it is unclear to what extent improvements in tic severity scores can translate to improvements in quality of life” is incorrect and potentially misleading. It ignores the result presented above for the C&A-GTS-QoL scale showing durable benefits for self-reported quality of life at both 12- and 18-month follow-up. It also disregards the ORBIT HTA report finding that reductions in YGTSS-TTSS scores map well to improvements in quality of life, detailed in the HTA cost effectiveness analysis https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10641713/ .<br><br>Furthermore, there is significant literature showing the impact of tic severity on quality of life https://link.springer.com/article/10.1007/s00787-016-0823-8 | |


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| | | | | Hence, stating that the impact of improved tic severity scores on quality of life is 'unclear' goes against both the evidence from the HTA report, our long-term follow-up data and existing literature in the field.<br>Finally, we wish to highlight that in the UK ORBIT trial, most secondary outcomes show improvement, even if that is only in the point estimate and they do not quite reach statistical significance. Importantly though, for 12- and 18-month outcomes, all point estimate outcomes favour ERP over psychoeducation, with 13/18 (>70%) reaching statistical significance. Notwithstanding, rather than being viewed as a weakness, or a marker of 'inconsistency', it's an important finding that the impact of the ERP intervention on global functioning and quality of life becomes stronger over time. Furthermore, ORBIT was not powered to detect a difference in the secondary outcome measures – which needs reflecting on in light of the report's statement regarding 'mixed results across secondary outcomes'. Hence, we feel the claims on this point should be rephrased or toned down throughout the report. We also feel these outcomes should be interpreted in light of the use of an active comparator rather than a wait list control. | |
| 39 | ORBIT study team University of Nottingham, NIHR MindTech HealthTech Research Centre | Abstract – Future studies | xii and p.84 | We disagree with the bold statement "*replication studies are required*" with respect to ORBIT and encourage the authors to specify the purpose and design of such replications. As already stated, the ORBIT trial replicates and builds on existing trial literature in the field both in the choice of an active comparator and selection of the primary outcome measure [https://jamanetwork.com/journals/jama/article-abstract/185896; https://jamanetwork.com/journals/jamapsychiatry/article-abstract/1307556]. | We believe that replication of results in diverse populations and outside the UK would increase the generalisability of results. |



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| | | | | The ORBIT trials were adequately powered and with low risk of bias, taken together demonstrate the efficacy of online ERP for tics (against an active online comparator) and durability of these benefits sustained up to 18months. We acknowledge that replications outside the UK are required to ensure generalisability of results to different populations and healthcare systems (e.g. with respect to ethnicity, internet access, patterns of co-morbidity, clinical severity and prevalence of different treatments in clinical populations). The Swedish replication suggests that culture and health system context may be important when translating results beyond the UK. However, we believe that the requirements for replication of the ORBIT trial in the UK – where NICE recommendations apply –would be firstly, a waste of scarce public resources as efficacy has already been demonstrated, secondly, unethical as it delays access to an effective intervention where no alternatives exist and thirdly, it is highly unlikely to be funded. We agree the priority now should be on the collection of real-world evidence data once ORBIT is implemented (see also the plans for the NIHR i4i PDA, funding ref: NIHR205467) and once new tic pathways are designed in England.<br><br>Due to heterogeneity of current patient pathways (in the absence of services in many parts of the country) a trial-based evaluation is unlikely to provide additional knowledge or reassurance beyond the current evidence base. It is more important to design appropriate pathways where the cheap and effective ORBIT intervention can start to address the chronic lack of capacity of services for this population. The UK ORBIT Trial (NIHR HTA funded) and the equivalent Swedish trial are the two largest RCTs in the field of | |



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| | | | | behavioural therapy for tics and have shown that online-delivered ERP is an effective intervention. Withholding an effective intervention in the pursuit of further replicating results not only seems unethical and delays access for those in need but elongates the process of establishing a service where there currently is none. Furthermore, it is unlikely that any funder would support this in the light of these two existing, fully powered RCTs. It's also unlikely that patients and referring clinicians would accept randomisation as clinical equipoise no longer exists.<br>Additionally, as the EAR's analysis revealed the studies were at low risk of bias, we would be grateful if the authors could clarify the need to replicate the study if this is the case. | |
| 40 | ORBIT study team University of Nottingham, NIHR MindTech HealthTech Research Centre | Abstract – Future studies | xii | We strongly disagree with the statement "*future studies should consider primary outcomes that measure impact on people's daily lives*". The YGTSS TTSS measures tic symptoms, including frequency, impact and severity and is the gold standard outcome measure in the field and was our primary outcome. While multiple primary outcomes are to be avoided in trials unless separate efficacy outcomes are anticipated – we included a range of relevant global measures of functioning and quality of life as secondary outcomes which demonstrated benefits for online ERP at long term follow-up.<br><br>The YGTSS-TTSS is internationally recognised as a valid and reliable measure of tics and tic treatment outcome. Please see this paper: https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2021.626459/full | This is our interpretation of findings. While it is important to show an improvement in severity of symptoms, we believe it is crucial to demonstrate that this improvement translates in better quality of life or improvement in activities of daily life and social interactions. Current evidence in the literature indicates that although YGTSS has acceptable psychometric properties, there is a need for further investigations and improvements. In fact, a revised version (YGTSS-R) has been recently developed. Moreover, current limitations of the global |


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| | | | | Additionally, systematic review evidence indicated that YGTSS is a recommended tic instrument https://movementdisorders.onlinelibrary.wiley.com/doi/full/10.1002/mds.26891?casa_token=zbjDYfiJ1QgAAAAA%3AtH5pQzNKOxZ8lZf8vd1eh7ea3QRohiOv8dfqCflgqdRBvCIHLXiURhmzh5u6hM4eYrzMmNvuemw38RIv<br><br>And further papers indicate its validity: https://psycnet.apa.org/buy/2005-16347-013<br><br>And its responsive to clinical change https://www.sciencedirect.com/science/article/pii/S1551714413001365?casa_token=kJrYg7z_Q6cAAAAA:qwIaQKxBwHOLp8_sLy9DqmWXE4MSamKWUIBNbfZAzj3eA68ptwGji_TirIE5YemwpyL1zNbqew<br><br>Hence, our choice of the YGTSS-TTSS as a single primary outcome replicates this consensus in the field. | severity score as a sum score indicate that separate use of the total tic score and the impairment score is preferable.<br><br>The review by Martino et al, which indicates that YGTSS is a recommended tic instrument is not systematic or methodologically sound. |
| 41 | ORBIT study team University of Nottingham, NIHR MindTech HealthTech Research Centre | Scientific summary and general | xiii | The line which states "*current practice varies between countries and according to availability of local services*" feels like it is missing a fundamental point – that is, the lack of access to tic disorder treatment services in the UK. How many patients can currently access a tic pathway or evidence-based care? There is a lack of responsibility for tic provision in many areas which typically leads to no treatment or delays in treatment.<br><br>We are currently undertaking an NIHR RfPB funded study "INTEND", led by Prof Maddie Groom from the University of Nottingham with Dr Charlotte Hall (ORBIT team) as co-applicant. We confidentially share some preliminary findings from INTEND with you to help further clarify the extent of this | Thank you for this information. |



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| | | | | problem. These findings are not yet available in the public domain.<br><br>FOI requests were sent to all 42 Integrated Care Boards (ICBs) in England, who were asked to complete the request on behalf of all of the geographical Places under their Board. Out of 42 ICBs covering 295 Places, sufficient responses were received from 34 ICBs that oversaw 234 Places. Seven out of 234 Places (3%) reported to have a standalone commissioned pathway for CYP with tics and a total of 10 services in England reported offering behavioural therapy for tic disorders. This highlights the current dire provision of tic services in England.<br><br>We asked whether Places wanted to improve their tic pathway, 151 Places responded to this and 117 Places (77.5%) were interested in receiving information about pathway recommendations, demonstrating a strong appetite for improved service provision.<br>We consider that the report needs to be revised to better reflect that the current standard treatment for tics is likely to be nothing, with only a few patients being able to access face-to-face behavioural therapy and many patients incurring healthcare costs as they seek treatment for their unmet need (see appendix). This vital context appears to be ignored by the authors of the report. | |
| 42 | ORBIT study team University of Nottingham, NIHR | Scientific summary and general | xiv | As we comment in the Abstract – methods section, why was the decision taken to replicate the ORBIT trial decision problem in the NICE model rather than consider the population of patients with diagnosed tic disorders as a whole. | Please see our response to the abstract point above. |



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| 43 | ORBIT study team University of Nottingham, NIHR MindTech HealthTech Research Centre | Scientific summary and general | xiv | We are unclear why it was considered appropriate to extend the time horizon beyond ten years given the level of uncertainty already inherent in the ten-year extrapolation. This is particularly questionable given differences between children's and adults' services and changes in tic severity during development. | We modelled a lifetime horizon in the base case as this reflects the NICE reference case that an economic model should capture all relevant costs and benefits of treatments. We agree that this introduces substantial uncertainty and that results of shorter modelled time horizons that we have conducted in scenario analyses may be more reliable. We have provided results over 2, 5 and 10 years. However, any decisions based on shorter time horizons should also acknowledge the lack of longer-term evidence and that the true cost-effectiveness remains unknown. |
| 44 | ORBIT study team University of Nottingham, NIHR MindTech HealthTech Research Centre | Throughout general | xv | With the line: '*In general, participants' engagement with the interventions, adherence and dropouts were reported to be similar between intervention groups'*.<br><br>It's worth noting that adherence to the ORBIT interventions weas excellent – as were scores on acceptability. This was shown across the UK and Swedish trials and is good evidence for the acceptability and uptake of the ORBIT intervention. | Thank you. These data are further reported in the intermediate outcomes section of our report. |



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| 45 | ORBIT study team University of Nottingham, NIHR MindTech HealthTech Research Centre | Abstract - Future research | xvii | The HTA report did compare ORBIT to face to face therapy – this needs to be acknowledged.<br><br>It is unclear the merit of comparing to a wait list control when an RCT with an active control has shown the intervention to be effective. It could seem unethical to withhold an effective intervention in order to see what the natural progression of a disease would be without an intervention. Case study evidence suggests that patients engage in an unstructured way with various health services while waiting which is costly for health services and deeply frustrating for patients (see appendix).<br><br>With regards to comparing sub-groups – ORBIT included analysis of comorbidity, sex and age: https://www.sciencedirect.com/science/article/pii/S2589979122000142<br><br>https://www.jmir.org/2021/6/e25470/<br><br>Please also see the Lancet Psychiatry and JCPP and HTA report for further analysis. This evidence should be cited and reflected on throughout the EAR and particularly in terms of how we have built on and extended a prior research base as we have previously stated. | We acknowledge that CBIT was included in the ORBIT modelling. However, this was based on assumptions about treatment effectiveness that were not supported by data (e.g. transition probabilities for CBIT were assumed equal to ERP beyond 6 months). We appreciate there is a lack of data regarding the clinical and cost-effectiveness of face-to-face therapy, which is why we chose not to include this as an arm in the economic model.<br><br>Considering tics in young people may improve over time, the inclusion of a wait list arm could provide information on the natural course of the disease. |
| 46 | ORBIT study team University of Nottingham, NIHR MindTech | Strengths, limitations and uncertainties | xvii | We disagree with the inclusion of the statement "*The reason(s) for selection of only the YGTSS-TTSS score as the primary outcome in the included studies, rather than the YGTSS-Impairment score, is unclear*."<br><br>As explained above, the YGTSS is considered a gold standard measure of tics, and the total tic score (TTSS) is | Thank you for your comment. If the YGTSS-Impairment score has weak psychometric properties it is unclear why has been included as a secondary outcome in all included studies. |



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| | HealthTech Research Centre | | | widely accepted in the field as the gold standard primary outcome measure both in trials and clinical practice. We also previously cite evidence to show that the YGTSS-Impairment score has weak psychometric properties and validity and therefore should not be used as a primary outcome. In summary, there is a clear and strong consensus internationally for use of the YGTSS-TTSS over the Impairment score, both in clinical and research settings. | Regarding the point about modelling face-to-face control, we refer to our response to point 45 above. |
| 47 | ORBIT study team University of Nottingham, NIHR MindTech HealthTech Research Centre | Characteristics of included studies | P16 | We respectfully disagree with the report authors regarding the following statement: "*Evidence was not available to compare the interventions under investigation and face-to-face behavioural therapy, the current standard of care*".<br><br>The HTA report used evidence from the literature to compare psychoeducation ORBIT to a face-to-face control. While face to face therapy may represent the ideal 'gold standard' behaviour intervention' because it is so rarely available and unfeasible to deliver at scale – it doesn't represent the current standard of care in any meaningful sense. In summary, although it maybe the theoretical gold-standard care, it is not the current standard of care that most young people receive – we have outlined this point more thoroughly above. Even if online ERP had a smaller effect size than F2F behavioural therapy – the head-to-head comparison in a trial is not informative for decision making as these interventions would be placed at different points in the care pathway with online ERP being a first-line highly scalable intervention with small incremental costs while F2F behavioural therapy is a second-line expensive, scare resource reserved for the most severe and/or treatment resistant cases, and is generally rarely available, and even then only in some regions (Cuenca et al, 2015 (https://pubmed.ncbi.nlm.nih.gov/25879205/) | We could not find any clinical effectiveness data related to the comparison between ORBIT and face-to-face therapy in the published articles and HTA report. It was therefore not possible to derive transition probabilities for the economic model. The EAG note that the modelled comparison in ORBIT relies on particularly strong assumptions of naïve comparison and assumptions of equivalence to ERP. To the EAG's knowledge, there is not evidence to support or refute these assumptions. |



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| | | | | Additionally, as outlined above, including a non-active control group is always likely to inflate the potential effectiveness of the intervention arm. Indeed, as the report acknowledges, our comparator (online psychoeducation) was a strong, active comparator and more than most patients are currently receiving. Thus, any advantages in the ERP group compared to this comparator are potentially even more impressive than a weaker/non-active control group. | |
| 48 | ORBIT study team University of Nottingham, NIHR MindTech HealthTech Research Centre | | P17 | The EAR reports the following uncertainty*: 'The proportion of participants with Tourette Syndrome in the UK ORBIT trial was not reported. The mean baseline tic severity measured using the YGTSS-TTSS scores was slightly higher in the UK ORBIT study than in the Swedish study; however, both trials described the participants' severity of tic disorders as moderate to severe'.*<br><br>In response, we would like to clarify that all participants in the UK ORBIT trial met criteria for a moderate or severe tic disorder (Tourette syndrome or chronic tic disorder). YGTSS-TTSS scores were slightly higher in the UK ORBIT trial than the Swedish trial and in other behavioural therapy trials for tics but are comparable with patients typically seen in UK clinical practice. In the UK ORBIT trial, the proportion of participants with chronic motor and vocal tics (equivalent to Tourette syndrome) was reported and was 92% and 95% in the two trial arms. | Thank you for the clarification. |
| 49 | ORBIT study team University of | | P17 | The report states uncertainty on the following point: '*It was unclear whether the participants in the two ORBIT trials had access to psychoeducation prior to recruitment into the trials.* | Thank you for this further information. |



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| | Nottingham, NIHR MindTech HealthTech Research Centre | | | *Access to psychoeducation was not an inclusion criterion for either trial'.*<br><br>We did not explicitly exclude or record whether participants had access to psychoeducation before the trial. However, given the lack of tic services in the UK, this is highly unlikely. As outlined in our HTA report, the ERP intervention also includes psychoeducation materials in the first 3 chapters, thus, both the ERP and psychoeducation arm receive some form of psychoeducation. After these chapters, the ERP group receive information about tic control (ERP), whereas the psychoeducation group receive further psychoeducation information.<br><br>Please also note, the eligibility criteria were the same across both arms (ERP v psychoeducation) and thus any impact of having prior psychoeducation on the effectiveness of the intervention would be balanced. | |
| 50 | ORBIT study team University of Nottingham, NIHR MindTech HealthTech Research Centre | Adverse events | 31 | We strongly disagree with the report's conclusion that there was limited reporting of safety evidence in the ORBIT trials. We respectfully request the report's authors to justify this statement in line with the available evidence and standards of adverse event (AE) reporting in the field. A recent systematic review explored AE reporting across digital trials, and compared to other trials of DMHI, ORBIT was superior in terms of AE reporting: https://mental.jmir.org/2023/1/e42501<br><br>In the Lancet Psychiatry Paper and HTA report (please see Table 10 in HTA report), we had a TSC and DMC which reviewed the adverse events and supported in categorising the SAEs in the control arm as unrelated (there were no SAEs in the intervention arm). | Thank you for pointing this out. The use of "limited" refers more to the lack of long-term data or those from the Neupulse study. We accept that long-term data may be difficult to interpret in terms of the nature of the interventions but feel it may be important in clinician/patient treatment decision-making. The adverse events in the two ORBIT studies are fully reported in our review. |



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| | | | | ORBIT included spontaneous and non-spontaneous (via an AE scale) reporting of AE reporting, which is more rigorous than most trials of a psychological intervention. Importantly, we continued to actively monitor AEs up to 6 months, which exceeds that of many trials. It is not uncommon for trials, including trials of drugs/devices to only measure during the duration of the intervention itself (See CONSORT harms statement for further reference to this point). Beyond this time frame, it becomes increasingly difficult to connect any recorded AEs to the intervention, especially to a behavioural treatment like ORBIT. The number of AEs recorded in each arm (note, no significant difference between the two) is testament to the rigour in which AEs were recorded. The reporting of harms in ORBIT conformed to the CONSORT harms checklist: https://www.acpjournals.org/doi/full/10.7326/0003-4819-141-10-200411160-00009?rfr_dat=cr_pub++0pubmed&url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org<br><br>Given the long-term follow-up (18 months) with continued symptom benefit and the thorough AE reporting for 6 months, “limited evidence” does not feel an accurate representation. We consider this should be re-worded to show that ORBIT was not associated with any related serious AEs, and the assurance of this categorisation provided by TSC and DMC should acknowledged.<br><br>Additionally, we question the validity in reporting long-term evidence beyond 6 months, as it would be very difficult to connect any AEs to treatment a year after they finished active participation, particularly given the range of other events that | |



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| | | | | may be occurring in a young person's life. Long term effects of a medication are potentially easier to link than a behavioural therapy given the differences in causal mechanisms of action between pharmacology and therapy. | |
| 51 | ORBIT study team University of Nottingham, NIHR MindTech HealthTech Research Centre | General | No specific page | Throughout the document refers to a lack of long-term evidence. This is incorrect and potentially misleading as in the UK the ORBIT trial has the longest controlled follow-up of exposure and response prevention for tics, regardless of digital/non-digital delivery: https://acamh.onlinelibrary.wiley.com/doi/full/10.1111/jcpp.13756 . We request that this should be acknowledged throughout. Furthermore, given the level of uncertainty in disease progression and clinical pathways, both SOC and proposed, it would be appropriate to restrict the economic evaluation to a shorter time frame and perhaps present results in a cost-consequence format. | We appreciate that the ORBIT follow-up data reflects the longest available data. However, the long-term effects of the interventions – positive or negative – may be important in making decisions about their use |
| 52 | ORBIT study team University of Nottingham, NIHR MindTech HealthTech Research Centre | Abstract - Future research | xvii and p.84 | The EAR makes several recommendations for future research that do not appear to consider prior work in the field as well as our existing and on-going work:<br><br>1) We are currently undertaking an NIHR i4i PDA where further real-world evidence will be gained – any future recommendations need to reflect this existing funded work which has already begun.<br>2) The HTA report did compare ORBIT to face-to-face therapy in terms of cost-effectiveness – this needs to be acknowledged when the future suggestion is to compare to face-to-face therapy. It also needs acknowledging that face-to-face therapy is the exception rather than the rule when it comes to current treatment (which is typically no treatment). | Thank you for alerting us to this ongoing work.<br>We acknowledge that the ORBIT modelling included a CBIT arm, but the effectiveness of this arm assumed that transition probabilities were equal to ERP after 6 months. This is a highly uncertain assumption and we felt it was not justifiable to include in our economic modelling.<br>Considering tics in young people may improve over time, the inclusion of a wait list arm could |


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| | | | | 3) It is unclear what is the purpose off comparing to a wait list control when an RCT has shown the ORBIT intervention to be effective against a more stringent active control. It could seem unethical to withhold this in order to see what natural progress on of a disease would be without an intervention. Case study evidence suggests that patients engage in an unstructured way with various health services while waiting which is costly for health services and deeply frustrating for patients. With regards to the need to compare sub-groups – ORBIT included analysis of comorbidity, sex and age: https://www.sciencedirect.com/science/article/pii/S2589979122000142 and https://www.jmir.org/2021/6/e25470/ Pease also see the Lancet Psychiatry (https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(21)00235-2/fulltext) and JCPP (https://acamh.onlinelibrary.wiley.com/doi/full/10.1111/jcpp.13756) and HTA report ((https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10641713) which report further sub-group analysis. | provide useful information on the natural course of the disease. |
| 53 | ORBIT study team University of Nottingham, NIHR MindTech HealthTech Research Centre | Model parameters – health state utility values | P62 | "*It is unclear whether child self-reports, parent proxy-report or a combination of both were used to derive health state utility values for application in the model*."<br><br>The base case uses parental values. This was specified in the Health Economics Analysis Plan as a greater response rate was expected from parents than from children. Sensitivity analysis looks at the children reported measures and resulted in higher effect on HR QoL overall. See this extract from the | Thank you for the clarification. We noted this for the within-trial QALYs but were unclear about how the HSUVs for the model were derived. In general, we would prefer the use of child-reported HSUVs in the economic model (even if completion was lower) and would be happy to incorporate |



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| | | | | Abstract of the HTA report [(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10641713]:<br><br>"Outcome: Primary outcome: Yale Global Tic Severity Scale-total tic severity score 3 months post-randomisation, analysis done in all randomised patients for whom data were available. Secondary outcomes included low mood, anxiety, treatment satisfaction and health resource use. Quality-adjusted life-years are derived from parent-completed quality-of-life measures. All trial staff, statisticians and the chief investigator were masked to group allocation". | these as a scenario analysis in the model if the ORBIT team wish to provide them. |
| 54 | ORBIT study team University of Nottingham, NIHR MindTech HealthTech Research Centre | Model parameters – health state utility values Evidence gaps | P62 | *"Evidence gaps: As demonstrated in the clinical-effectiveness review, the relationship between tic severity and HRQoL is unclear. Changes in the clinical outcome do not necessarily lead to changes in quality of life or health state utility values".*<br><br>There is an abundance of literature showing the impact of tic severity on quality of life https://link.springer.com/article/10.1007/s00787-016-0823-8 Stating that the impact of improved tic severity scores on quality of life is 'unclear' goes against both the evidence from the HTA report and existing literature in the field. We comment on this also previously (see above). As noted above, the UK ORBIT trial showed benefits of online ERP on the GTS-QoL scale at 12- and 18-months follow-up. | Please note that our statement relates to the uncertainty regarding the magnitude of impact on CHU-9D utilities that could be derived from a one-point difference in the YGTSS-TTSS score, and in particular, uncertainty around the magnitude of change in the score that would translate into QALY benefits. We accept that there is a correlation and that this has been included in the economic modelling. Indeed, this is evident from lower HSUVs in the more severe tic states included in the model. |
| 55 | ORBIT study team University of | Interpretation of evidence and | P83 | The statement "*the fact that there were no improvements in the YGTSS-Impairment score casts some doubt on whether a reduction in tic severity translates into an improvement in daily life*" is not accurate and potentially misleading as it gives | Thank you. As noted in our report, changes in quality-of-life scores were also inconsistent. Taken together, we feel it is |



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| | Nottingham, NIHR MindTech HealthTech Research Centre | conclusions | | undue precedence to a single global functioning secondary outcome measure (YGTSS-Impairment scale) with weak psychometric properties to the exclusion of others scales included in the NICE scope (e.g. CGI-I, C-GAS, C&A-GTS-QoL scale) .<br><br>There was a clear reduction in impairment in both treatment groups and the difference between them was just short of statistical significance. See evidence presented earlier on both % reductions in YGTSS Impairment scale as well as other secondary outcomes. At the end of the study both groups were rated as having mild impairment following either ERP or psychoeducation. These positive findings in both conditions are likely attributable to the use of an active comparator with human support and the shared elements of psychoeducation. However, notwithstanding the impact of the active control psychoeducation in reducing impairment, significant benefits of online ERP on global functioning and quality of life (measured by CGI-I, C-GAS and C&A-GTS-QoL scale) were reported at 12- and 18-months follow-up.<br><br>We ask that this is rephrased as there should be no doubt that “reduction in tic severity translates into an improvement in daily life”, as this translation is clearly demonstrated in our HTA report and the existing literature.<br><br>The statement “*Therefore, for the ORBIT studies, it was not possible to separate the effects of online delivery from those of ERP*” is incorrect. The use of an active online control condition (supported psychoeducation) meant that we were able to isolate the effects of ERP separately from online support. | justifiable to suggest there was no association between improvement in tic severity and improvement in daily life. Meta-analysis of YGTSS-Impairment scores at 3- and 12-months in the two ORBIT trials showed results that did not reach the level of statistical significance. In addition, impairment scores were lower than baseline at 12 months in the Swedish ORBIT study, demonstrating the inconsistency of changes in scores. |



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<table>
<tr><td>56</td><td>ORBIT study team University of Nottingham, NIHR MindTech HealthTech Research Centre</td><td>General</td><td></td><td></td><td></td></tr>
<tr><td colspan="5">

**APPENDIX – anonymised case studies of access to care**

**Confidential**

**Healthcare utilisation and costs associated with poor access to diagnosis and treatment for children and young people with tic disorders**

**Table 1: Anonymous report from [redacted] on their experience (adapted from patient's report)**

| Date | Description | Cost (In 2023 GBP) |
|---|---|---|
| [redacted] | [redacted] | [redacted] |

</td><td>Thank you. Please see response to point 28 above.</td></tr>
</table>



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| | | | | |
| [redacted] | [redacted] | [redacted] | | |
| Total | | [redacted] | | |

[redacted]

**Table 2: Anonymous report from [redacted] on their experience (adapted from patient's own report)**

| Date | **Description** | Cost (In 2023 GBP) |
|---|---|---|



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| | | | | [redacted] | |
| | | | | Total [redacted] | |
| 57 | Jeremy Stern St George's Hospital | General | | Whilst YGTSS is a considered a gold standard and is inevitably available in trials, the 5 point Impairment score of the YGTSS is a crude ordinal in steps of 10 up to 50 not fully characterised on p14, depends on potentially informal and often rapidly assessed self-reported mood effects/impairment and is not well validated as a responsive measure of improvement/change. The high level results / conclusion summary (eg at pages xii and xv, 84 and others) citing a null change in this measure do not convincingly indicate the implied implication on quality of life effects. | Please see our previous responses on this point. |
| 58 | Jeremy Stern | General | xviii | Absence of comparator of face-to-face behavioural therapy- an obvious valid research point but in terms of service | Please see our previous responses on this point. |



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| | St George's Hospital | | | delivery the availability of face-to-face behavioural therapy is also virtually absent in the NHS (as acknowledged on p4) so the "standard of care" is not currently a practical alternative to online delivery which may be more possible to provide. | |
| 59 | Jeremy Stern St George's Hospital | | P61 | Haloperidol is very little used in the UK although has a BNF indication, not significant in the cost analysis but clinically not relevant | Thank you for this clarification point. We can confirm that removing haloperidol from the list of considered treatments in the scenario analysis, which includes medication costs, would have minimal impact on results. |
| 60 | Stacey Chang-Douglass | General | NA | Please ensure all tables have abbreviation list where relevant. Currently some tables in the EAR have an abbreviation list, but some don't. | Thank you. We will review the report and make the necessary amendments. |
| 61 | Stacey Chang-Douglass | Economic model overview, *Table 14 Summary of the economic model* | p. 63 of PDF | Table 14: "*Personal communication with the company suggested no direct set-up or training costs involved.*" It is unusual that no set-up or training costs involved as company suggested, especially digital interventions may require the patients/ health care professionals to familiarise the new platform etc. This is likely to be a discussion point at the committee meeting. | Thank you for this comment. We agree that this should be discussed, and we can provide scenario analyses if helpful for the Committee. |
| 62 | Stacey Chang-Douglass | Economic model overview, *Table 16 Modelled population characteristics for* | p. 69 of PDF | Distribution for mean age and % of male: currently the distribution of these two model inputs is marked as "fixed" in table 16. Do you mean they are not varied? Or do you mean they are varied in the PSA, such as Gamma or Beta distributions? Please consider revising the notes in table 16 if needed. | We mean they are not varied. |



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| | | *ORBIT and Neupulse evaluations* | | | |
| 63 | Stacey Chang-Douglass | Economic model overview, *Table 17 Transition probabilities [reproduced from Hollis et al., 2023, Table 17]* | p.71 of PDF | For each row of table 17, the numbers should add up to 100%. However, some rows don't add up to 100%, e.g. row 3 (from Moderate) added up to 99.8%. Please kindly check. | Thank you for checking these numbers. We can confirm that the issue relates to rounding errors when transferring the economic model output to rounded data for the report. We have cross-checked the economic model and can confirm that all probability parameters sum to 100%. |
| 64 | Stacey Chang-Douglass | Economic model overview, *Table 20 Summary of health state costs applied in the model.* | p.79 of PDF | Rows for "very mild" and "mild" have the same base case and scenario values (mean, SE etc.) Is this intentional? If we are not expecting difference between base case and scenario values in these two rows, please consider removing the "scenario" row(s). | Thank you for this comment. We can confirm that the scenario analysis applies including medication costs has no impact on the health state costs for mild or very mild states as clinical expert advice suggested that drug treatment would only be provided for moderate to severe tics. |
| 65 | Stacey Chang-Douglass | Economic model overview | p. 80 of PDF | "*At any given time, the UK general population norm is calculated using the method described by Ara and Brazier (2010).*" NICE DSU published new methods report on a more updated approach of estimating UK general population norm. | Thank you for this comment. We have explored the impact of using the most recent approach from the DSU report and can confirm that the impact on cost- |



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| | | | | Please see the relevant report at the link below and revise the estimates in your model as required: https://www.sheffield.ac.uk/nice-dsu/methods-development/estimating-eq-5d | effectiveness results is minimal. Table 1 below compares the base case deterministic ICER for ORBIT vs. psychoeducation from the EAG report, using the Ara and Brazier approach to UK general population norm calculation with the updated approach from the NICE DSU. The impact on the ICER is minimal (<£50). |
| 66 | Stacey Chang-Douglass | Results – ORBIT, Figure 10 and 11 Markov cohort traces Results – Neupulse Figure 14 and 15 Figure 17 CEAC | p. 87, p. 94 and p.96 of PDF | If possible, please change the line style to smooth line in these figures. | Thank you for this comment. The final report will be edited to include smoothed figures. |
| 67 | Stacey Chang-Douglass | Scenario analysis Figure 18-19 Two-way scenario analysis | p. 97-98 of PDF | Please revise the axis titles of these two figures. Currently they are showing the TreeAge programme model input names, which are difficult for readers to interpret what the axis are. | Thank you for this comment. Revised figures with updated axis titles are provided as Figures 1 and 2 below (reproducing Figures 18 and 19 of the EAG report). |



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| 68 | Stacey Chang-Douglass | General | NA | The data gap texts are included across different parts of the report. However, it would be useful to have a summary of the key data gaps, preferably in a table format with traffic light colour-coded overview, please. Also, if it's possible, please add any relevant information about ongoing research. | |

## Table 1 Impact of different approaches to calculating UK general population norms on cost-effectiveness results

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) |
|---|---|---|---|---|---|
| **EAG base case, deterministic ICER** | | | | | |
| Psychoeducation | £12,755 | 20.916 | - | - | - |
| ERP | £12,974 | 20.939 | £218 | 0.024 | £9,289 |
| **Apply updated NICE DSU approach to general population utility norm calculation.** | | | | | |
| Psychoeducation | £12,755 | 21.225 | - | | |
| ERP | £12,974 | 21.248 | £218 | 0.023 | £9,334 |


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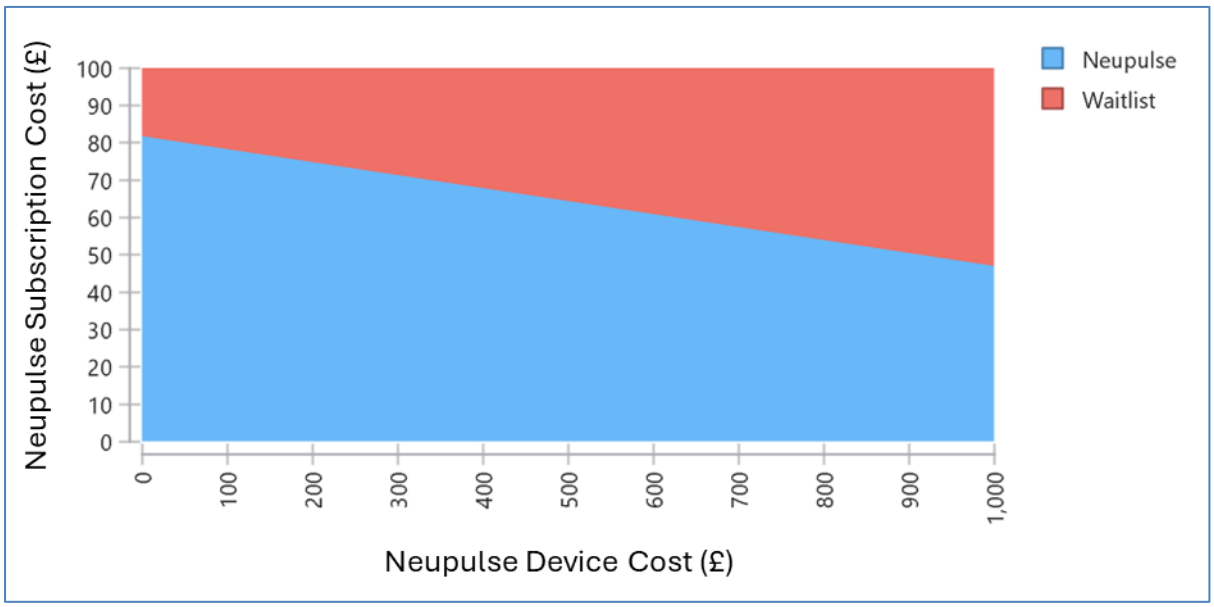


**Figure 1: Two-way scenario analysis of initial and subscription costs for Neupulse (assumes long-term transition probabilities extrapolated) [re-produces Figure 18 of the EAG report]**

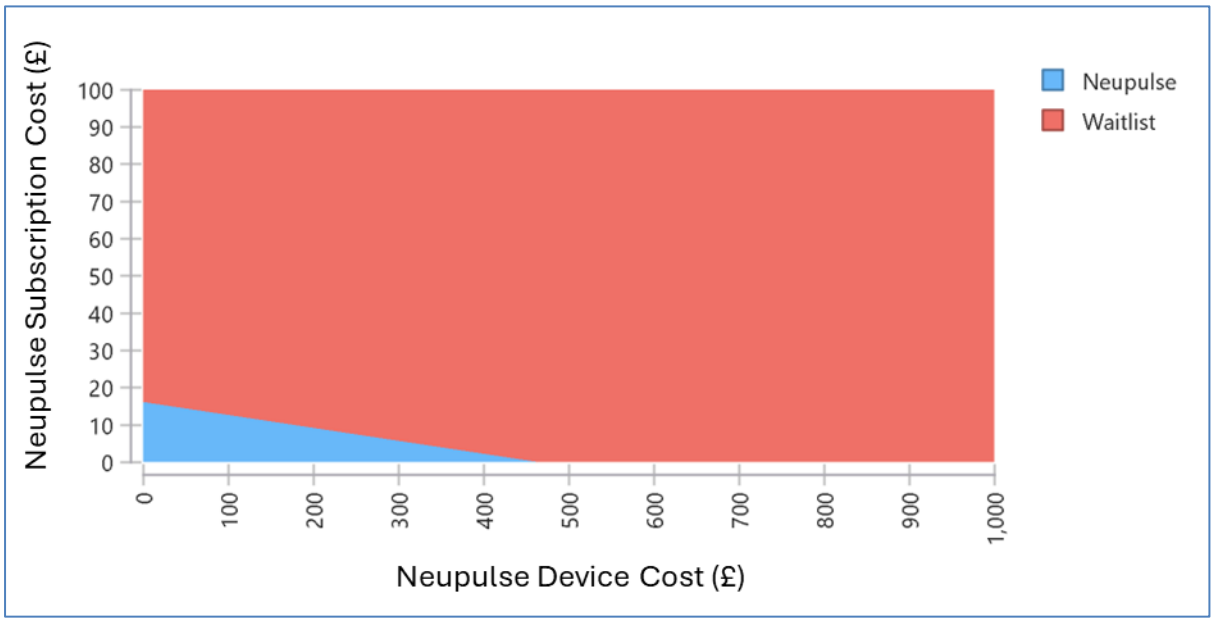


**Figure 2: Two-way scenario analysis of initial and subscription costs for Neupulse (assumes cohort held in last observed state) [re-produces Figure 19 of the EAG report]**



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NICE National Institute for Health and Care Excellence

# Medical Technologies Advisory Committee Interests Register

**Topic: Digitally enabled therapy for chronic tic disorders and Tourette Syndrome**

**NICE's declaration of interest policy can be accessed here**

| Name | Role with NICE | Type of interest | Description of interest | Interest arose | Interest declared | Interest ceased | Comments |
|---|---|---|---|---|---|---|---|
| Harriet Stuart | Specialist Committee Member | Financial Interest | Private Practice | 2023 | 10.11.2023 | Ongoing | No further action |
| Harriet Stuart | Specialist Committee Member | Non-Financial professional & personal interests | Fellow of Royal College of Psychiatrists | 2020 | 10.11.2023 | Ongoing | No further action |
| Harriet Stuart | Specialist Committee Member | Non-Financial professional & personal interests | Board member of Psychiatric Bulletin RCPsych | 2017 | 10.11.2023 | Ongoing | No further action |
| Inyang Takon | Specialist Committee Member | Financial Interests | I undertake Private practice at Portland Hospital London, Rivers Hospital Sawbridgeworth and Centennial Medical Care | 2007 | 05.12.2023 | Ongoing | No further action |

| Name | Role with NICE | Type of interest | Description of interest | Interest arose | Interest declared | Interest ceased | Comments |
|---|---|---|---|---|---|---|---|
| | | | **Director- Zaneil Limited- Healthcare company providing neurodevelopmental services** | | | | |
| Inyang Takon | Specialist Committee Member | Financial Interests | **I am a co-founder of school doctor- Social enterprise that provides neurodevelopmental services to schools and families. Involved in training for parents and schools and also consultations. www.school-doctor.com** | 2015 | 05.12.2023 | Ongoing | No further action |
| Inyang Takon | Specialist Committee Member | Financial Interests | Co-author of a book- 'ADHD Tics and Me' | 2022 | 05.12.2023 | Ongoing | No further action |
| Inyang Takon | Specialist Committee Member | Non-Financial professional & personal interests | CAMHS Lead – East and North Hertfordshire NHS Trust | 2017 | 05.12.2023 | Ongoing | No further action |
| Inyang Takon | Specialist Committee Member | Non-Financial professional & personal interests | Specialist expert- NICE Quality standards on FASD | 2019 | 05.12.2023 | 2022 | No further action |

| Name | Role with NICE | Type of interest | Description of interest | Interest arose | Interest declared | Interest ceased | Comments |
|---|---|---|---|---|---|---|---|
| Inyang Takon | Specialist Committee Member | Non-Financial professional & personal interests | Principal Investigator on an Industry funded trial on ADHD medication. PI for the East and North Herts Trust | 2020 | 05.12.2023 | Ongoing | No further action |
| Inyang Takon | Specialist Committee Member | Non-Financial professional & personal interests | Committee member on FASD Experts Committee – FASD committee advocating for improved national awareness on Foetal Alcohol Spectrum Disorder. Developed usefiul training materials along with other professional, parents and carers | June 2021 | 05.12.2023 | Ongoing | No further action |
| Tara Murphy | Specialist Committee Member | Financial Interest | Consultant Psychologist and team lead for Tic disorder service, Great Ormand St Hospital | October 2020 | 4.12.2023 | Ongoing | No further action |
| Tara Murphy | Specialist Committee Member | Financial Interest | Consultant Psychologist and team lead for Tic disorder service, Great Ormand St Hospital | Sept 2012 | 4.12.2023 | July 2017 | No further action |
| Tara Murphy | Specialist Committee Member | Financial Interest | Consultant Psychologist leading private practice under Tara Murphy LTD | June 2006 | 4.12.2023 | Ongoing | No further action |

| Name | Role with NICE | Type of interest | Description of interest | Interest arose | Interest declared | Interest ceased | Comments |
|---|---|---|---|---|---|---|---|
| Tara Murphy | Specialist Committee Member | Financial Interest | I have written several books about Tourette's syndrome and other neurodevelopmental/Neuropsychological for which I receive royalties (approx. £300 per Annum) | 2016 | 4.12.2023 | Ongoing | No further action |
| Tara Murphy | Specialist Committee Member | Financial Interest | I have been co-applicant on the following relevant grants:<br><br>Research for patient Benefit programme: NIHR204897 – Improving Tic Services – A mixed methods study to co-design a service model for children and young people with Tourette syndrome<br><br>Clinical translation and commercialisation of ORBIT creating a patient ready product to improve access to behavioural therapy for children and young people with tic disorders | 1ST Nov 2023<br><br>1st April 2024 | 4.12.2023 | 31st January 2024<br><br>March 2027 | Declare and participate - verbal declaration in committee meeting |

| Name | Role with NICE | Type of interest | Description of interest | Interest arose | Interest declared | Interest ceased | Comments |
|---|---|---|---|---|---|---|---|
| | | | Remotely delivered behavioural intervention for tics in children and adolescents with Tourette syndrome. 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 | Sept 2016 | | April 2021 | |
| Tara Murphy | Specialist Committee Member | Non-Financial professional & personal interests | I have co authored several publications describing research on digital technologies in treatment of Tourette syndrome | 2010 | 4.12.2023 | ongoing | No further action |
| Tara Murphy | Specialist Committee Member | Indirect Interests | I am recently appointed trustee of Tourette action, the national UK charity for Tourette syndrome | Dec 2023 | 4.12.2023 | Dec 2026 | Declare and participate - verbal declaration in committee meeting |

| Name | Role with NICE | Type of interest | Description of interest | Interest arose | Interest declared | Interest ceased | Comments |
|---|---|---|---|---|---|---|---|
| Jeremy Stern | Specialist Committee Member | Financial Interests | Medical private practice adult neurology | 2005 | 12.06.2024 | Ongoing | No further action |
| Jeremy Stern | Specialist Committee Member | Non-Financial professional & personal interests | Trustee/director of Tourette's action | | 12.06.2024 | Ongoing | Declare and participate - verbal declaration in committee meeting |
| Emma McNally | Expert | Non-Financial professional & personal interests | CEO Tourette's action | Jan 2022 | 10.01.2024 | Ongoing | Declare and participate - verbal declaration in committee meeting |
| Samantha Bramley | Lay Specialist committee member | Financial Interests | Taking part in paid research group for INTEND Improving Tic Services in England | 09.12.2023 | 10.01.2024 | Ongoing | No further action |

| Name | Role with NICE | Type of interest | Description of interest | Interest arose | Interest declared | Interest ceased | Comments |
|---|---|---|---|---|---|---|---|
| Joanne Dooley | Lay Specialist committee member | Non-Financial professional & personal interests | Manchester Tourettes Support Group volunteer | 2015 | 05.06.2024 | 2024 | No further action |