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Digitally enabled therapy for chronic tic disorders and Tourette Syndrome in children and young people [GID-MT605]

Name of External Assessment Group (EAG) and project leads

Aberdeen Health Technology Assessment Group

Miriam Brazzelli
Professor (Research)
Health Services Research Unit (HSRU)
University of Aberdeen
Health Sciences Building, Foresterhill
Aberdeen AB25 2ZD
Tel: 01224 438181
Email: m.brazzelli@abdn.ac.uk

Dwayne Boyers
Senior Research Fellow (Health Economics)
Health Economics Research Unit
University of Aberdeen
Polwarth Building, Foresterhill
Aberdeen AB25 2ZD
Tel: 01224 437850
Email: d.boyers@abdn.ac.uk

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Plain English Summary

Tic disorders involve fast, irregular, and repetitive muscle movements that can be in any part of the body. Motor tics involve body movements such as blinking and grimacing while vocal or phonic tics involve repetitive sounds such as grunting or sniffing. Typically, tic disorders manifest during childhood, while the brain is still developing, generally at around five years of age. The severity of tic disorders can vary and the impact on people's health and wellbeing can be significant. Some tic disorders do not last long while others continue for over 12 months, and these are called persistent or chronic tic disorders. People with Tourette syndrome have multiple motor tics and at least one vocal tic. People with chronic tic disorders often have other mental health conditions, such as obsessive-compulsive disorder or attention deficit hyperactivity disorder and anxiety.

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, as treatments are provided by a limited number of specially trained staff, children and young people may wait a long time before getting access to them. Treatments that can be delivered remotely using digital technology may represent a possible solution. Nevertheless, we need to know whether these treatments are better than the treatments currently available for controlling tics.

The purpose of this assessment is to gather information on the use of digital technologies for the treatment of chronic tic disorders and Tourette syndrome among children and young people. We intend to determine if these treatments are effective and if they represent good value for money. We are planning to compare the costs, such as the cost of treatment, and the benefits, such as the severity of symptoms and quality of life, of the existing treatments to establish the best use of NHS resources. This will help inform clinical practices and policies.

1. Decision problem

1.1 Purpose of the decision to be made

The National Institute for Health and Care Excellence (NICE) is evaluating the clinical and cost-effectiveness of digitally enabled therapy for children and young people with tic disorders. This is due to the potential benefit of digitally enabled therapy in addressing the significant unmet needs of the population.

Current guidance in the UK 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.[1] Non-pharmacological treatment options for confirmed tic disorders include psychoeducation as a first-line intervention and behavioural therapy for those who continue to experience difficulties with their tic disorders. Current evidence-based behavioural therapy approaches comprise habit reversal therapy (HRT), comprehensive behavioural intervention for tics (CBIT) and exposure and response prevention therapy (ERP). 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 children and young people with tic disorders have access to it.[2] In the UK, digitally enabled interventions have the potential to improve access as well as equity of access to treatment for children and young people with tic disorders,

1.2 Description of the technologies

The technologies considered for this appraisal are digital technologies that enable the remote/online delivery of therapeutic intervention to children and young people with chronic tic disorders or Tourette Syndrome. 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. In total, two digitally enabled technologies, **Online Remote Behavioural Treatment for Tics** and **Neupulse** to treat children and young people with chronic tic disorders have been identified for this assessment.

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 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.[3-5] 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.[4, 5] ORBIT does not require CE marking as it is not considered a medical device. At present, the investigators are working towards DTAC compliance.

Neupulse (Neurotherapeutics) is a wearable digital wrist device with a corresponding phone app, which proposes a novel approach to help reduce tic frequency and severity. The device, currently in development, produces median nerve stimulation (MNS) to reduce tic frequency and tic intensity in Tourette Syndrome whilst the device is active and in a follow-up period without the device activated.[6] Delivery of rhythmic patterns of mild electrical stimulation to the median nerve at the wrist has been shown to increase brain activity associated with movement suppression, which substantially reduced the frequency of tics and urge to tic. Intentional movement and cognitive function were not impaired.[7, 8] The device requires no active effort by the user but is worn when the user wants to feel more control of their symptoms. The device is proposed for children and young adults aged 12 and over, 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. Neupulse is currently working towards CE and UKCA marking, and it is estimated that the device will be available in 2026. 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.[6]

1.3 Population and relevant subgroups

The population under consideration is children and young people with chronic tic disorders or Tourette Syndrome. We will accept the definition of 'children' and/or 'young people' as reported by the authors of the included studies. Studies including a mixed population (adults and children/young people) will be considered eligible for inclusion and data for children and young people will be extracted, where possible.

Where data permit, the following subgroups may be 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 (only for studies that include a mixed population of children and adults)

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

Test name	ORBIT (MindTech)	Neupulse (Neurotherapeutics)
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.	Unclear
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: 1. Learn about tics/introduction 2. More about tics/thoughts and behaviours of supporters 3. Practising stopping your tics/praise 4. Making the practice more challenging/prompts 5. Continued practice/situations and reactions 6. School/troubleshooting 7. Talk about your tics/continued practice 8. Continued practice/continued practice 9. The final sprint/continued practice 10. Plan for the future/plan for the future	Median nerve stimulation (Morera Maiquez Preprint: *The intensity of stimulation (1-19 mA) was individualised for each participant based on the approach previously used in Morera et al. (2020).*[9] *Specifically, the stimulation threshold for each participant was determined by delivering single pulses to the wrist at increasing intensity until a visible contraction in the thenar muscle was observed. In the active group, a session of stimulation consisted of delivering rhythmic pulse trains of MNS at a frequency of 10Hz in which each pulse was of 200 µs (i.e., 0.2 ms) duration and was delivered at 120% of motor threshold, in bursts of 2 minutes of stimulation followed by 1 minute of no stimulation. This was repeated 5 times, lasting 14 minutes in total. Stimulation was delivered on the wrist of their right hand. To ensure that the participants were wearing the device during stimulation, the device only operated if it was correctly attached to the wrist. The device was also restricted so that it could only be used once each day.*)[7]
Aim of therapy	ERP aims to break the urge-tic-relief cycle of reinforcement whilst promoting tolerance of premonitory urges and tic suppression.	Reduce tic frequency and tic intensity in Tourette syndrome
Duration	10 weeks.	Unclear (in the Morera Maiquez trial, participants used the device at home for 14 minutes daily for one month – participants were not necessarily children)[10]

Test name	ORBIT (MindTech)	Neupulse (Neurotherapeutics)
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.	N/A (wearable device) The Morera Maiquez: trial states that *"to ensure that all participants underwent daily sessions of stimulation, the device incorporated software that updated the research team after each use."*[7]

1.4 Clinical condition of interest

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.[11-14] 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).[15]

The mean age of onset for tic disorders is approximately 5 years, although it can be lower in up to 40% of patients.[14, 16] Typically, the severity of tic disorders worsens between 10 and 12 years of age and improves naturally during adolescence and early adulthood.[17, 18] In children and young people, tics tend to come and go, while in adults, they show a more persistent pattern.[19] Psychiatric comorbidities are common among people who suffer from chronic tic disorders.[20] People with Tourette syndrome or chronic tic disorders often experience associated psychiatric conditions such as ADHD (30 to 54% of people) and OCD (10% to 50% of people).[21] 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).[16, 21] Comorbid mood disorders tend to be observed more frequently in adolescents and adults than children.[22] Independent from ADHD and OCD comorbidities, Tourette syndrome has also been reported to be associated with an increased risk of anxiety.[16]

Internationally, the prevalence of Tourette Syndrome in young people in the community has been reported to be between 0.4% and 3.8%.[12] A meta-analysis of 13 studies published in 2012

reported a pooled prevalence rate of 0.77% (95% CI 0.39 to 1.51) in children[23]. In the UK, Tourette Syndrome is identified in 1 per 100 school children.[24]

Tic disorders can vary in severity and impact various aspects of children's and young people's lives, contributing to a reduced quality of life. It is not uncommon for young people with tic disorders, particularly when the illness is more severe, to experience serious social issues such as extensive stigma and bullying.[20] Severe long-lasting tic disorders are also associated with a fourfold increased risk of suicide.[2]

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

1.5 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.[25-27] 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 in adults and children.[1] 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.[22, 24, 28, 29]

Symptoms of tic disorders may be reported by the children or young people themselves or identified by their parents/carers or school educators. In the UK, children and young 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, a referral is usually made to NHS secondary care services including the Children and Young People's Mental Health Services (CYPMHS).[2]

As tics may improve with time, the NICE Guideline 127 indicates that for children and young people presenting in primary care a watch-and-wait approach is considered acceptable, especially for those who do not experience any functional impairment.[1]

Children and young people with tic disorders that have a significant impact on their quality of life should be referred 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.

Current practice varies between countries and according to the availability of local services but, in general, treatment options for chronic tic disorders in children and young adults include psychoeducation, pharmacological therapy, behavioural 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.[24] In many cases, children and young people 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.[2]

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.[30-32] 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.

Current international guidelines recommend the use of **behavioural therapy** as the first-line intervention for tic disorders in children and young people.[22, 28, 29, 33] 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).[22] 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.[29]

Deep brain stimulation (DBS) in specialised centres has been proposed for patients with severe tics that are refractory to behavioural and pharmacological interventions.[22, 24] 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.[29] The largest available RCT conducted in adults indicates some possible benefits but also highlights several methodological challenges in the design of stimulation studies.[22, 34, 35]

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 for children and young people 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.[36]

1.6 Aim and Objectives

This assessment aims to address the following research question:

Are non-pharmacological interventions delivered remotely/online better than standard care as currently implemented in clinical practice?

The main objectives of this assessment are the following:

- To evaluate the safety and effectiveness of digitally enabled non-pharmacological therapy for treating chronic tic disorders and Tourette Syndrome in children and young people 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 in children and young people that are available or likely to become available soon in UK clinical practice.

2. Evidence synthesis methods

The eligibility criteria for the review of clinical effectiveness evidence are summarised in Table 2 below. Methods related to the development of the economic model are described in Section 3.

Table 2 Eligibility criteria for the review of clinical effectiveness evidence

Population of interest	Children and young people diagnosed with a confirmed primary, chronic tic disorder
Clinical condition	Primary, chronic tic disorders including Tourette Syndrome. Transient and secondary tic disorders will not be considered eligible for inclusion. Similarly, functional tic-like behaviours are beyond the scope of this assessment.
Technologies under investigation	• ORBIT (MindTech) • Neupulse (Neurotherapeutics)
Comparator intervention	Standard care, including psychoeducation and face-to-face behavioural therapy.
Outcome measures	**Intermediate outcome measures** • Intervention-related adverse events • Treatment satisfaction and engagement • Intervention adherence, rates of attrition and completion **Clinical outcome measures** • Measures of symptom severity (self, parental or practitioner reported) using validated instruments such as YGTSS, TTSS • Social, behavioural, and functional outcomes • Suicidal thoughts and behaviour **Patient-reported outcome measures** • Health-related quality of life • Patient's experience and patient's satisfaction • 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. We will include RCTs, and comparative non-randomised studies published in English. Crossover studies will also be deemed eligible for inclusion but only the data from the phase before the crossover will be utilised. If there is not sufficient evidence from comparative studies, we will also consider evidence from uncontrolled studies. Articles available in their pre-publication version and relevant reports submitted by the manufacturers of the technologies under investigation will also be considered for inclusion. Conference abstracts will be excluded because they are not considered to provide sufficient information. However, if potentially relevant conference abstracts are identified, we will investigate whether fuller information is available from another source.
Healthcare setting	Secondary care setting (e.g., CYPMHS) Tertiary care settings (e.g., neurology or neurodevelopmental teams - including neurologists, neuropsychologists, psychiatrists, psychologists, specialist nurses, speech and language therapists).

2.2 Search methods for identification of studies

A sensitive literature search strategy will be developed by an Information Specialist to identify published peer-reviewed studies. Major electronic databases will be searched, including MEDLINE, Embase, Cochrane Library, Web of Science, and CINAHL. The search will focus initially on the approved devices listed in the NICE final scope; search facets defining the population of interest will be included. There will be 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 will be screened for additional studies. Major clinical trial registries will be searched to identify relevant ongoing trials. Websites of manufacturers of relevant technologies, professional organisations, regulatory bodies and HTA organisations will be searched to identify additional relevant reports. Any additional information on potentially relevant evidence provided by the manufacturers of the technologies of interest will also be considered. All references will be exported to Endnote for recording and deduplication. A draft MEDLINE search is detailed in Appendix 1. The MEDLINE search will be adapted to search other electronic databases.

2.3 Study selection and data extraction strategies

One reviewer will screen the citations identified by the search strategies. A second reviewer will independently screen a random sample of citations (20%). Potentially relevant articles will be retrieved in full. Two reviewers will independently assess each article for eligibility based on the pre-specified inclusion criteria. We will resolve any disagreement by discussion or consultation with a third reviewer. Multiple publications of the same studies will be linked and considered together. For excluded studies, we will document reasons for exclusion. We will illustrate the study selection process through a PRISMA flow diagram.

Two reviewers will independently extract data from each eligible study using a customised form developed for this assessment. Any disagreements will be resolved by discussion or consultation with a third reviewer.

The following information will be 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.

2.4 Quality assessment strategy

We will use the Cochrane risk of bias tool for the assessment of randomised trials evaluating the clinical utility of the automated devices under investigation.[37] For assessing the quality of non-randomised evidence reporting quantitative data on the effectiveness of the technologies under investigation we will use the checklist developed by the HSRU, University of Aberdeen, in partnership with the NICE Review Body for Interventional Procedures (ReBIP). The ReBIP checklist was adapted from several sources[38-41] and comprises 17 items, which assess the following aspects: generalisability, sample definition and selection, description of the intervention, outcome assessment, adequacy of follow-up, and performance of analyses.

One reviewer will extract the data and a second reviewer will check the data extracted. Any disagreements will be resolved by consensus or consultation with a third reviewer.

2.5 Methods of analysis/synthesis

When appropriate, we intend to summarise the results of relevant RCTs and observational studies evaluating the clinical effectiveness of digitally-enabled therapy in children and young people with chronic tic disorders using standard meta-analysis methods.[37] We will consider a narrative synthesis of results if considerable clinical and methodological heterogeneity is observed between studies. A detailed description of any gaps in the evidence will be provided together with any methodological limitations of the existing studies. This will help inform recommendations for future research and requirements for a full assessment.

3. Report methods for synthesising evidence of cost-effectiveness

The economic evaluation for this assessment aims to assess the potential cost-effectiveness of digitally enabled therapies compared to standard care for children and young people with tic disorders. The specific health economic objectives are:

- to review and critically appraise existing economic evaluations of treatments for people with chronic tics.
- to develop a decision analytic model that can be used to assess the cost-effectiveness of digitally enabled therapy, compared with standard care. Where insufficient data are available to populate the model (e.g., if it is not possible to build a network of evidence in line with the NICE scope comparators), the economic model will be used to identify the key drivers of cost-effectiveness and to prioritise areas for future research to reduce residual uncertainty regarding the optimal treatments.

3.1 Identifying and systematically reviewing published cost-effectiveness studies.

Systematic search strategies will be developed to identify full economic evaluations of digitally enabled therapies for people with tic disorders. The following databases will be searched, with no time, language, or publication type restriction:

- Ovid MEDLINE
- Ovid EMBASE
- NHS Economic Evaluations Database
- International HTA Database (INAHTA)
- Research Papers in Economics
- Cost-Effectiveness Analysis (CEA) Registry

A draft MEDLINE search strategy is included in Appendix 1 and will be adapted for the other included databases. The websites of relevant professional organisations (e.g., ISPOR Scientific Presentations Database) and health technology agencies such as NICE, CADTH, PBAC, ICER and others, will be referenced for supplementary reports. Furthermore, reference lists of all incorporated studies will be manually reviewed to identify additional relevant studies. Additional data and information provided by the companies will be assessed for relevance to the decision problem and will be included in results summaries where appropriate.

The review will include full economic evaluations with population, intervention and comparators as described in Table 2 above. 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 will be included.

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

The appropriateness of full economic evaluations for addressing the research questions specified in the NICE final scope will be assessed. If deemed suitable, study authors of included decision modelling studies (e.g., the ORBIT study) will be contacted to request access to model files, which could be adapted or re-populated for this assessment.

3.2 Development of a health economic model

A decision analytic model will be developed to assess cost-effectiveness of the candidate interventions compared with standard care for children and young people with chronic tic disorders. The model will, where possible report incremental cost per quality-adjusted life year (QALY) gained over a lifetime horizon from a UK NHS and personal social services (PSS) perspective. Costs and outcomes will be discounted at 3.5% per year in line with the NICE reference case.

Should insufficient data exist from the clinical effectiveness reviews to populate a full assessment of cost-effectiveness, the model will be used to identify the key parameter drivers of cost-effectiveness. In such a scenario, a combination of multi-way scenario analyses (including threshold analyses) and value of information analyses will be used to identify priority areas for future research to resolve any residual uncertainties in the cost-effectiveness evidence base.

3.3.1 Model structure

The specific details of the model type, pathway, and structure will be developed either by adapting an existing model (e.g., the ORBIT study model)[5] or developing a new *de novo* model using existing evidence. The conceptual cost-effectiveness model structure will be developed following the current NICE methods guide[45] and will be validated with the EAG and NICE clinical expert advisors for this assessment. We envisage that we will build a Markov cohort-based model, with health states reflecting tic severity (e.g., mild, moderate, severe tics), defined according to a tic severity outcome measure such as YGTSS to make best use of the existing evidence base. Clinical validation of the model structure may require several iterations and adaptions and will ensure that the model structure demonstrates good face validity, ensuring that it appropriately reflects the current NHS practice and pathway.

3.3.2 Model parameterisation

The base case model structure will be parameterised to reflect the gold standard care pathway, based on available clinical guidelines.[22, 24, 28, 29] An alternative parameterisation, reflecting current standard of care in UK clinical practice will also be explored if required, reflecting that current standard of care may not align with best practice recommendations.

The model will be populated with data on transition probabilities sourced from the literature; intervention costs obtained from the companies, operating manuals and supplementary literature; and health state costs and utilities from the literature. Additional targeted searches will be undertaken, where appropriate, to inform the choice of key model parameters (e.g., health state resource use and utilities). Where multiple sources of parameter estimates exist, priority will be given to data from systematic reviews (or updates of existing reviews) that are consistent with the NICE reference case, followed by other published literature. Where sufficient published data are not available, we will use data from conference presentations and clinical expert elicitation as necessary to populate key model parameters.

Treatment effect sizes for application to the modelled health states (e.g. relative risk [RR] of health state occupancy) will be obtained from the systematic review of clinical effectiveness studies where these data are available. As the modelled health states are likely to be derived based on a dichotomisation of the YGTSS tic severity scale, not all studies may report data in a format that aligns with the intended economic model structure. When this is the case, we will contact authors directly requesting access to data in a format that aligns with the ideal

model structure. Where such data are not available, we will explore a range of assumptions and alternative economic modelling structures to make the best use of the available clinical effectiveness data.

Resource use and costs associated with intervention delivery, adverse events, long-term routine management and health state specific costs will be identified based on data provided by the companies and a review of current clinical guidelines, published data, and clinical expert opinion. A micro-costing of the interventions and standard care will be conducted. This will include device costs, additional training costs, and staff resource costs. Resource use data for intervention delivery will be sought from the companies, product manuals and literature. Resource use data for routine management will be obtained from national guidelines for the base case, with clinical expert opinion used in scenario analysis to assess variation in the management of tics across the UK. All resource use data will be costed using nationally available average unit costs.

As NICE does not recommend specific measures of HRQoL in children and young people, we will assess the most appropriate measure to inform health state utility values based on an assessment of the measure's validity and the best available data from the literature. Where possible, we will derive health state utility values from the CHU9D for children. The CHU9D has been validated for use in child and adolescent mental health services and aligns with our inclusion criteria for children (ages 5 to 11) and young people (ages 12 to 18) as it is designed for individuals aged 7–17 years and has a UK value set. Where sufficient data exist, we will also explore whether other measures of HRQoL can be considered in the modelling (e.g. GTS-QoL).

3.3.3 Analyses and reporting of results

The base case results of the model will be presented in terms of expected total costs, LYs, QALYs and incremental cost per QALY gained over the modelled time horizon. The model will be fully probabilistic. Results will be presented as pairwise comparisons of each intervention vs. standard care. A fully incremental analysis of multiple interventions will also be provided. Cost-effectiveness acceptability curves will be used to illustrate the probability that each intervention is the optimal treatment strategy at different threshold values of willingness to pay for a QALY gained. Scatter plots of pairwise comparisons on the cost-effectiveness plane will be used to further illustrate the magnitude of parameter uncertainty.

We acknowledge that generic QALYs may not be sufficiently sensitive to capture processes and outcomes of care that are important to chronic tics and patients with Tourette syndrome. If possible, we will also endeavour to report model outcomes using a measure of change in clinical outcome over the modelled time horizon (for example, the incremental cost per additional case of severe tics avoided).

We anticipate a lack of robust data across multiple assumptions and parameters for this assessment. To populate parameters where data are not available, we will heavily rely on the opinion of clinical experts. This approach may introduce a considerable level of uncertainty, which we will address through a range of deterministic sensitivity and scenario analyses. Where data allow, subgroup analyses will be performed in line with those outlined in Section 1.3 above.

4. Handling information from the companies

Following a request for information, any 'commercial in confidence' data provided by a company and specified as such will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company name e.g., in brackets). Any academic-in-confidence data provided will be highlighted in yellow and underlined. Only information received by 1 June 2024 will be considered for inclusion in the assessment report.

5. Competing interests of authors

None

5. References

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Appendix 1 Literature search strategies

MEDLINE search for the review of clinical effectiveness evidence

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions

1	exp Tic Disorders/ or (tic or tics).tw,kw.
2	exp Behavior Therapy/
3	((psychological or behavio* or cognitive) adj5 (therap* or intervention?)).tw,kw.
4	("Habit Reversal Training" or HRT or "Comprehensive Behavio?ral Intervention for Tics" or "Exposure and response prevention" or ERP).tw,kw.
5	Internet/ or Online Systems/ or Internet-Based Intervention/ or Mobile Applications/ or Cell Phone/ or Smartphone/ or telemedicine/
6	(digital or remote or online or web or internet or technology).tw,kw.
7	(2 or 3 or 4) and (5 or 6)
8	Wearable Electronic Devices/ or ((wearable adj7 (technolog* or device?)) or wearables).tw,kw.
9	(ORBIT or Mindtech or Neupulse or Neurotherapeutics).af.
10	1 and (7 or 8 or 9)

MEDLINE search for the review of cost-effectiveness evidence

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to January 12, 2024>

1	exp Tic Disorders/ or (tic or tics).tw,kw.
2	exp Behavior Therapy/
3	((psychological or behavio* or cognitive) adj5 (therap* or intervention?)).tw,kw.
4	("Habit Reversal Training" or HRT or "Comprehensive Behavio?ral Intervention for Tics" or "Exposure and response prevention" or ERP).tw,kw.
5	Internet/ or Online Systems/ or Internet-Based Intervention/ or Mobile Applications/ or Cell Phone/ or Smartphone/ or telemedicine/
6	(digital or remote or online or web or internet or technology).tw,kw.
7	(2 or 3 or 4) and (5 or 6)

8	Wearable Electronic Devices/ or ((wearable adj7 (technolog* or device?)) or wearables).tw,kw.
9	(ORBIT or Mindtech or Neupulse or Neurotherapeutics).af.
10	1 and (7 or 8 or 9)
11	exp "costs and cost analysis"/
12	*economics/
13	economics, hospital/
14	exp economics,medical/
15	economics,pharmaceutical/
16	exp models, economic/
17	exp decision theory/
18	monte carlo method/
19	markov chains/
20	exp technology assessment, biomedical/
21	(cost$ adj2 (effective$ or utilit$ or benefit$ or minimis$)).ab.
22	economics model$.tw.
23	(economic$ or pharmacoeconomic$).tw.
24	(price or prices or pricing).tw.
25	budget$.tw.
26	(value adj1 money).tw.
27	(expenditure$ not energy).tw.
28	markov$.tw.
29	monte carlo.tw.
30	(decision$ adj2 (tree? or analy$ or model$)).tw.
31	ec.fs.
32	or/11-31
33	10 and 32