
# Diagnostic Assessment Report commissioned by the NIHR Evidence Synthesis Programme on behalf of the National Institute for Health and Care Excellence

## Final Protocol

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# Plain English Summary

## What is the problem?

Attention deficit hyperactivity disorder (ADHD) is a common condition that affects behaviour in both children and adults. People with ADHD may find it hard to concentrate, act without thinking and be unable to sit still. This can get in the way of daily life.

ADHD is usually diagnosed by a specialist (an expert in ADHD) based on the person's history, behaviour and symptoms. The expert will typically observe the person and interview the person and others in their life (e.g. partners, parents or teachers).

It can take a long time to be diagnosed with ADHD and the person may have to go to lots of appointments. ADHD is also sometimes confused with other mental health conditions that have similar symptoms, making it harder to diagnose.

New tests have been developed that may improve how ADHD is diagnosed and followed up. These tests involve the person doing a computer-based task which measures behaviours associated with ADHD (e.g. ability to concentrate and to control movement). These tests may reduce the number of appointments needed and could increase the likelihood of diagnosing ADHD correctly. They might also be able to help work out if treatments are working properly.

## What are we trying to find out?

We want to know whether using these new tests to help diagnose ADHD will mean that more people are correctly told whether or not they have ADHD, and whether the tests can be used to correctly tell us how well ADHD treatments work. We also want to know whether using these tests is a good use of NHS money.

## What are we going to do?

We will review existing research and develop cost models to answer these questions.

# 1 Background and Decision Problem

## 1.1 Epidemiology and burden of ADHD

Attention Deficit Hyperactivity Disorder (ADHD), is a neurodevelopmental disorder characterized by persistent patterns of inattention, impulsivity, and hyperactivity that can significantly impact daily functioning.[1] Different subtypes can be defined based on these key features:

- Inattentive subtype
- Hyperactive-impulsive subtype
- Combined subtype (both inattentive and hyperactive-impulsive)

The exact cause of ADHD is unknown but is generally considered to involve multiple genetic and environmental factors that lead to altered brain neurochemistry and structure. ADHD is estimated to affect around 2 to 7% of school-aged children and young people, with an average estimate of around 5%.[2] There has been a substantial increase in the proportion of children diagnosed with ADHD over the past 30 years, with rates doubling between 2003 and 2018.[3] Increasing awareness of ADHD among healthcare professionals, educators, and the general public has contributed to higher rates of diagnosis.[2] ADHD often persists into adulthood - studies suggest that around 15% of adults will continue to meet full diagnostic criteria for ADHD, 65% will continue to show symptoms which impact on their life, whereas around 20% will have no symptoms or impairment in adulthood.[4] Certain population may be more likely to have ADHD – a 2018 meta-analysis estimated that up to 1 in 4 prisoners had a diagnosis of ADHD,[5] although a more recent re-analysis of this data reported that, after accounting for an outlier and restricting to studies that used random sampling of adults in prison, prevalence was much lower at around 4.5% in men.[6]

ADHD can have a significant impact on individuals' academic, social, and occupational functioning. Children with ADHD may struggle in school, have difficulty forming and maintaining relationships, and experience low self-esteem.[7, 8] In adulthood, untreated ADHD can lead to challenges in employment, relationships, and mental health.[9] Symptoms of inattention can make even basic tasks such as reading, watching television and multi-tasking challenging.[10] Among adults, there is an expectation of being able to function independently but difficulty maintaining attention can make this very challenging.[10] However, there are also positive effects of ADHD, with a recent qualitative study highlighting that sometimes acting on impulse can have positive effects leading perhaps to a fulfilled and exciting life.[10] The burden of ADHD extends beyond the affected individuals to their families, schools, and the healthcare system – a UK based study highlighted the impact of ADHD on the quality of life of children with ADHD and of their siblings.[7] The economic burden includes healthcare costs, educational support services, and lost productivity for individuals and caregivers.

ADHD is usually diagnosed in childhood, with symptoms often becoming noticeable when a child starts school.[11] Boys are more commonly diagnosed with ADHD than girls, with a male-to-female ratio estimated at around 3:1.[2, 12] People with ADHD may seem restless, have trouble concentrating and may act on impulse.[11] Boys present differently from girls – they

often display disruptive behaviour prompting referral, whereas girls are more likely to have the inattentive subtype, making it less likely for girls to be referred for evaluation of ADHD. Symptoms of ADHD may change with age, with symptoms relating to hyperactivity improving whilst those relating to inattentiveness persist.[4, 13]

## 1.2 Current diagnostic and care pathway

### 1.2.1 Referral

The NICE guideline on ADHD diagnosis and management (NG87) provides guidance on the diagnostic pathway for ADHD.[14] However, this can be seen as best practice and is not always reflected in reality in the NHS. The guidance suggests that children and young people with suspected ADHD should be referred from community settings to secondary care for further investigation – this is often to a paediatrician with more complex cases referred to child and adolescent mental health services (CAHMS). Community referral is usually made by a health, education, or social care professional, for example the GP, educational psychologist, or school special educational needs coordinator. Exact referral and care pathways vary locally.[14]

NICE guidelines recommend that adults presenting with symptoms suggestive of ADHD who do not have a childhood diagnosis of ADHD should be referred to secondary care for further assessment by a mental health specialist with training in the diagnosis and treatment of ADHD. Referral is usually made from primary care or general adult psychiatric services. Adults who were diagnosed and treated for ADHD as children, or people who present with symptoms suggestive of continuing ADHD, should be referred for further assessment.[14]

The following groups have a higher likelihood of having ADHD than the general population, and so a lower threshold for referral may be appropriate in these groups:[14]

- people born preterm
- looked-after children and young people
- children and young people diagnosed with oppositional defiant disorder or conduct disorder
- children and young people with mood disorders
- people with a close family member diagnosed with ADHD
- people with epilepsy
- people with other neurodevelopmental disorders (e.g. autism spectrum disorder, tic disorders, and learning difficulties)
- adults with a mental health condition
- people with a history of substance misuse
- people known to the Youth Justice System or Adult Criminal Justice System
- people with acquired brain injury.

The guidelines also highlight that ADHD is likely to be under-recognised in girls and women who may be less likely to be referred for ADHD assessment, may be less likely to be

diagnosed with ADHD and may be more likely to receive an incorrect diagnosis of another mental health or neurodevelopmental condition.[14]

### 1.2.2 Diagnosis

Assessment and diagnosis of ADHD is a complex process that typically relies on a clinician's judgment and involves gathering information from multiple sources, such as assessment questionnaires, third-party reports, patient history, and behavioural observations. This approach is largely subjective and can lead to concerns regarding the reliability and consistency of the diagnosis.[15] It is also resource intensive - it usually takes an average of 2 to 3 appointments and around 2.5 hours of clinic time to reach a diagnosis of ADHD.[16] Guidelines from The Royal College of Psychiatrists in Scotland suggest that in most cases the assessment and diagnosis of ADHD in adults will require 2 to 3 one hour sessions.[17] Whilst children are usually assessed face-to-face in clinic, assessment for adults is often done remotely. This avoids the need to travel long distances to centralised assessment centres and also means that family members can join the consultation from different locations. Waiting times for a diagnosis through the NHS can also be lengthy - a recent survey suggested that 10% of respondents had been waiting between 2 and 3 years for an ADHD assessment and 24% had waited between 1 and 2 years.[18] Our clinical advisors from Avon and Wiltshire Mental Health Partnership NHS Trust (AWP) report that waiting times are currently around 18 months for referrals to be triaged and then a further 5 years to obtain a diagnosis. The average time to diagnosis in children is reported to be 18 months.[19]

The NICE guideline on ADHD diagnosis and management (NG87) recommends diagnosis based on a combination of psychosocial assessment, patient history, symptoms and behaviour.[14] To make a diagnosis of ADHD, symptoms of hyperactivity/impulsivity and/or inattention should meet the diagnostic criteria of DSM-5 or ICD-11[20, 21] and should cause at least moderate psychological, social and/or educational impairment. This should be based on interview and/or direct observation in multiple settings. Impairment should be pervasive occurring in at least 2 important settings including social, familial, educational and/or occupational settings.[14] The guidance highlights that the diagnosis should only be made by a specialist psychiatrist, paediatrician or other appropriately qualified healthcare professional with training and expertise in the diagnosis of ADHD.[14]

ADHD is frequently associated with other neurodevelopmental and psychiatric conditions. Common co-occurring conditions include autism spectrum disorders (ASD), personality disorders, learning disabilities, anxiety disorders, mood disorders, conduct disorders and developmental trauma.[1] The presence of these comorbidities can complicate the diagnosis and management of ADHD.[4] Diagnosis can also be more challenging amongst those in the criminal justice system.

A number of rating scales are available to help diagnose ADHD. The most commonly evaluated rating scales include Achenbach System of Empirically Based Assessment (ASEBA), Conners Scales, DSMIV based ratings scales (e.g., the ADHD Rating Scale IV), and the

Strengths and Difficulties Questionnaire (SDQ). A recent systematic review of these tools concluded that although most tools have excellent overall diagnostic accuracy (area under the curve, AUC, ranged from 0.76 to 1.00), a single measure completed by a single reporter is unlikely to have sufficient accuracy for clinical use.[22] This finding is reflected in the NICE guidelines, which state that a diagnosis should not be made solely on the basis of such scales.[14]

Other tests that can help with the diagnosis include Continuous Performance Tests (CPT). These are computer-based tests that assess an individual's sustained attention and impulse control. Examples of these tests include: Test of variables of attention (TOVA), Gordon's diagnostic system (GDS) and Conners' CPT. These tests are designed to be used alongside clinical assessment as part of the diagnostic pathway for ADHD. A systematic review found mixed evidence on the clinical utility of CPT as an assessment tool. They highlighted that such tests should not be used as a stand-alone diagnostic tool and suggested that combining CPTs and an objective measure of activity may be particularly useful as a clinical tool and worthy of further pursuit.[23] These tests are not explicitly mentioned in the NICE guidelines.

### 1.2.3 Management and treatment of ADHD

Managing ADHD requires a multidisciplinary approach, with NICE guidance recommending that individuals with ADHD should have a comprehensive, holistic shared treatment plan that addresses psychological, behavioural and occupational or educational needs.[14] The treatment plan should be developed through discussion with those affected by ADHD and their families – this should be an ongoing process and should undergo regular review. Recommendations on treating ADHD vary according to age, with slightly different recommendations for those under 5 years, children and young people aged over 5 years and adults. Treatment plans will be tailored to the individual but are likely to encompass some or all of the following:[24]

*Behavioural Interventions*: Behavioural therapies are used to improve organizational skills, impulse control, and self-regulation. Parent training and classroom management strategies are often included.

*Educational Support*: For children and young people, schools are encouraged to provide support, such as Individual Education Plans (IEPs) and accommodations to address academic challenges.

*Psychosocial Support*: Individual or family counselling may be recommended to address emotional and psychological issues.

*Lifestyle and Self-Care*: Encouraging a healthy lifestyle with regular exercise, a balanced diet, and adequate sleep is important. Developing structured routines and organization skills can also be beneficial.

*Awareness and Education*: Parents, caregivers, and individuals with ADHD are provided with education and support to help them understand the condition and learn strategies for managing symptoms.

*Medication*: Medications, such as stimulants (e.g., methylphenidate or amphetamine-based drugs) or non-stimulants (e.g., atomoxetine, guanfacine, clonidine), may be prescribed based on the severity of symptoms and individual response.[25]

Medication should only be given to those with ADHD if their symptoms are still causing persistent impairment after alternative support strategies have been implemented.[14] However, due to the length of time that it currently takes to receive a diagnosis, medication is often started soon after diagnosis. Medication is not recommended in those under 5 without a second specialist opinion, ideally from a tertiary centre.[14] Before starting medication a detailed baseline assessment is required. Medication is usually started at a low dose that is gradually increased as needed.[24] The optimal dose will balance treatment effectiveness against severity of any adverse effects. Potential adverse effects vary according to which medication is prescribed but include: small increases in blood pressure, decreased appetite, trouble sleeping, headaches, stomach aches, drowsiness, dizziness, diarrhoea, nausea and vomiting and mood changes including feeling aggressive, irritable, depressed, anxious or tense.[24] Treatment is considered optimal when patients demonstrate reduced symptoms, positive behaviour change, improvement in education, employment, and relationships, with tolerable adverse effects. Achieving optimal treatment requires regular review, assessment, and adjustment of medication.

Once a patient has started treatment, NICE guidelines recommend regular monitoring to assess effectiveness and adverse effects. They recommend that those taking medication should record adverse events, ideally using an adverse effect checklist. Treatment effectiveness should be monitored using standard symptom and adverse effect rating scales.[14] There are two stages to monitoring treatment effectiveness. The initial stages is during the dose titration phase, when patients are seen approximately every 2 weeks, until they are on a stable dose of medication. After this they are monitored annually, mainly to assess whether the treatment remains effective.

## 1.3 Technologies of interest

Technologies of interest for this appraisal include technologies that combine measures of cognition and motor activity for the assessment of ADHD. Technologies are eligible if they are available to the NHS and have appropriate regulatory approval.[26]

### 1.3.1 QbTest (QbTech Ltd.)

The QbTest is a class I medical device designed for diagnosing ADHD and managing treatment in those with ADHD aged 6 to 60 years. It has received CE marking, indicating its compliance with European Union medical device regulations. It combines computerised assessments with a high-resolution motion tracking system to evaluate three core symptoms of ADHD: attention, impulsivity, and hyperactivity.

The QbTest involves a computer-based task that typically takes 15 to 20 minutes to complete. During the test, the individual is required to respond to specific stimuli by pressing a button. To monitor motor activity during the test, the individual wears a headband. This motion tracking system records and measures hyperactivity and other motor-related behaviours. To administer the QbTest, a private and quiet room with a computer, desk and chair is needed. Trained healthcare assistants or nurses can oversee the test, and a trained clinician interprets the results. Test results are compared to a normative group of individuals of the same sex and age who do not have ADHD. Outputs of the test are visually reported, detailing the performance in each of the three symptom domains of ADHD (activity, attention, and impulsivity) and the level of deviation from non-ADHD score and are sent directly to the clinician. Results are expressed as the Q-Score for sub-categories of activity, impulsivity and inattention. Q-scores reflect the deviation of the participant's performance (in standardised units) from the mean score of the normative group. There is no standard threshold for defining a positive Q-score as the scores are only meant to inform the diagnosis – the clinician combines the QbTest data with questionnaire responses and observational information for a comprehensive assessment.

The QbTest was implemented across 69 NHS trusts between 2020 and 2023 as part of an Academic Health Science Network (AHSN) initiative known as "Focus ADHD" which aimed to improve the diagnosis of ADHD in children and young people.[19] An evaluation of the Focus ADHD programme based on an audit of clinics using the QbTest reported that time from assessment to diagnosis was reduced by 153 days, 85% of patients reported that they found the QbTest results helpful, 94% of clinicians reported that they had a greater understanding of patients' symptoms, and the return of investment was estimated at almost £6 for every £1 spent.[27] However, this evaluation was not a formal comparison of the clinical effectiveness of the QbTest against standard clinical care. A recent NICE Medical Innovation Briefing highlighted that the QbTest could be used as an addition to routine clinical assessment, not as a standalone test. It also highlighted uncertainties in that the evidence reviewed included potentially inappropriate populations and did not use a parallel clinical assessment. It suggested that the technology was likely to be cost saving due to clinician time saving and efficiency of the pathway - however, the briefing did not include a formal economic evaluation of the evidence.[28]

### 1.3.2 QbCheck (QbTech Ltd.)

QbCheck is related to the QbTest but is designed for remote testing and can be used without a healthcare professional present. Like the QbTest it is a class I medical device, indicated for use as an online diagnostic tool and for treatment management in people aged 6 to 60 years. It combines an online computerised continuous performance task (CPT) with a webcam motion tracking system and, like the QbTest, results are compared to a normative group without ADHD, with results reported in the same way as for the QbTest.

The QbCheck requires a laptop or computer with a stable internet connection in an appropriate location. The test can be administered and observed by trained healthcare assistants or nurses and interpreted by a trained clinician alongside questionnaire responses and observational data.

### 1.3.3 EFSim Test (ARVO) (Peili Vision Company)

The EFSim is a virtual reality (VR) game designed for children and young people aged 8 to 13 years. It is CE marked as a class I medical device. It involves completing everyday tasks within a simulated home environment and is intended to be used alongside existing clinical assessments for ADHD.

The game consists of a 25-minute in-game session played on an Oculus Go head-mounted display and its hand controller. During gameplay, motion tracking sensors in the goggles and controller capture the participant's movements. An updated version of the EFSim Test that includes eye movement (saccades) tracking is due to be available in early 2024.The test assesses various performance indicators related to ADHD, including attention, hyperactivity, impulsivity, memory, time management, planning, behaviour regulation, task efficiency, and efficiency of information processing.

A web-based, remote version of the EFSim Test is also in development. This is due to be available in early 2024.

### 1.3.4 Nesplora Attention Adults Aquarium (Giunti psychometrics)

The Nesplora Attention Adults Aquarium is a CE-marked, virtual reality continuous performance test (VR-CPT) suitable for people aged 16 to 90 years. It measures symptoms of ADHD including auditory and visual attention, impulsivity, motor activity and reaction time. It is intended to be used alongside current ADHD clinical assessment.

The test involves an 18 to 22 minute computerised task that is conducted whilst wearing a VR headset and headphones. It requires a virtual reality device, computer, stable internet connection, and headband headphones. The person undertaking the test uses a handheld button to respond to both visual and auditory stimuli. Results are available immediately, and are visually reported, detailing a score for the following categories: attention, inhibitory control (impulsivity), motor activity, processing speed, distractibility, and vigilance. This score is calculated by comparing to a normative data set of people without ADHD of the same sex and age. All measures for sustained attention and inhibition are obtained separately for auditory and visual modalities and for the two modalities combined.

### 1.3.5 Nesplora Attention Kids Aula (Giunti psychometrics)

The Nesplora Attention Kids Aula is a CE-marked VR-CPT. It is very similar to Nesplora Attention Adults Aquarium but is aimed at young people aged 6 to 16 years – the test also involves a computerised task, measures the same ADHD symptoms as the adult version and is performed and interpreted in the same way as the adult version.

## 1.4 Place of the technology in the diagnostic and treatment pathway

There are four potential roles for the new technologies in the diagnostic and treatment pathway. In all cases, the tests should be used alongside healthcare professional assessment:

1. As part of the initial diagnostic assessment for all people referred with suspected ADHD
2. As part of the initial diagnostic assessment for people where a diagnostic decision cannot be reached using current assessment methods.
3. To assess medication effectiveness during initial dose titration and treatment decisions in people with a diagnosis of ADHD
4. To assess treatment (pharmacological or non-pharmacological) effectiveness for long-term treatment monitoring for people with a diagnosis of ADHD

# 2 Aim and Objectives

The overall aim of this project is to determine whether technologies for objective measures of ADHD that use motion sensors to measure hyperactivity are clinically and cost-effective to the NHS. We have identified the following objectives to address this aim:

1. What is the diagnostic accuracy and clinical- and cost-effectiveness of technologies that combine measures of cognition and motor activity for the diagnosis of ADHD in people referred with suspected ADHD?
2. What is the diagnostic accuracy and clinical- and cost-effectiveness of technologies that combine measures of cognition and motor activity for the diagnosis of ADHD in people referred with suspected ADHD for whom current assessment cannot reach a diagnosis?
3. What is the clinical- and cost-effectiveness of technologies that combine measures of cognition and motor activity in evaluating medication effectiveness during initial dose titration and treatment decisions for people with a diagnosis of ADHD?
4. What is the clinical and cost-effectiveness of technologies that combine measures of cognition and motor activity for evaluating treatment effectiveness during long-term treatment monitoring for people with a diagnosis of ADHD?

# 3 Methods for the clinical effectiveness review

A systematic review will be conducted to summarise the evidence on the clinical effectiveness, diagnostic accuracy and technical performance of technologies that combine measures of cognition and motor activity for diagnosis and management of ADHD. The systematic review will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care, the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy and the NICE Health Technology Evaluations Manual.[29-31] The review will be reported according to PRISMA-2020, PRISMA-DTA and PRISMA-E guidelines.[32-34]

## 3.1 Inclusion and exclusion criteria

Studies that fulfil the following criteria will be eligible for inclusion:

### 3.1.1 Technology (intervention/index test)

QbTest, QbCheck, EF Sim, EF Sim Web Version, Nesplora Kids and Nesplora adults alone or in combination with clinical assessment for ADHD by a health care professional.

### 3.1.2 Population

*Objective 1*: Adults and children referred for evaluation of suspected ADHD
*Objective 2*: Adults and children referred for evaluation of suspected ADHD in whom a diagnosis has not been made through standard assessment processes
*Objective 3*: Adults and children with a diagnosis of ADHD undergoing initial dose titration and treatment decisions
*Objective 4*: Adults and children with a diagnosis of ADHD being monitored for treatment effectiveness

### 3.1.3 Setting

Secondary care or remote assessment setting will be eligible.

### 3.1.4 Comparator

Any diagnostic assessment for ADHD that does not include the technology of interest. Studies that compare two or more technologies of interest will also be eligible for inclusion. For evaluation of diagnostic test accuracy, studies that report a direct comparison of the accuracy of one of the technologies of interest and other CPT (e.g. Connor's CPT) will also be eligible.

### 3.1.5 Reference standard (diagnostic accuracy studies only)

Any reported diagnostic assessment for ADHD.

### 3.1.6 Study designs

For assessment of *clinical effectiveness* we will include randomised controlled trials (RCT) or non-randomised study of interventions (NRSI). For evaluation of *diagnostic test accuracy*,

we will include diagnostic test accuracy (DTA) studies of any design including one gate (also known as diagnostic cohort or cross-sectional studies) and two gate (also known as diagnostic case-control studies) designs. Qualitative studies will also be eligible if they provide data on any of the specified outcomes. Where data are not available on any of the specified outcomes from the designs listed, we will also consider UK based observational studies that include a control group (e.g. before-after study).

### 3.1.7 Outcomes:

Studies will be required to report at least one of the following outcomes of interest for this appraisal:

- Test performance (diagnostic accuracy) e.g. sensitivity, specificity, area under the ROC curve (AUC)
- Test failure
- Time to assessment or to reach a diagnostic decision
- Use of NHS and PSS services (such as the number and length of clinical appointments prior to diagnosis)
- Impact on clinical decision-making
- Confidence of healthcare professionals in assessment
- Ease of use/acceptability for clinicians
- Use of interventions (such as ADHD medication)
- Morbidity
- Mortality
- Health related quality of life
- Ease of use/acceptability for patients or carers
- Patient and carer experience
- Costs related to using the technologies
- Cost of training staff to operate technology and interpret results
- Costs of resources associated with diagnosing and reviewing ADHD
- Cost of interventions to help manage ADHD Heath-related quality of life

Existing systematic reviews will be included if they fulfil inclusion criteria, are judged as low risk of bias based on the ROBIS tool,[35] have searches conducted within the past year, and stratify the synthesis as described in our synthesis section (section 3.5), otherwise they will be used a source of potentially relevant studies. If we identify relevant reviews that meet these criteria, literature searches will still be conducted as outlined below to ensure that relevant primary studies are not missed.

## 3.2 Study identification

Studies will be identified using bibliographic and non-bibliographic search methods following guidance in the NICE Health Technology manual.[30]

### 3.2.1 Bibliographic searching

The following databases will be searched:

- MEDLINE (Ovid SP)
- EMBASE (Ovid SP)
- PsycINFO (Ovid SP)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) (EBSCOhost)

We will use a sensitive search strategy based on terms for each of the technologies eligible for inclusion and for the manufacturers of these technologies. A draft search strategy is reported in Appendix 1.

### 3.2.2 Non-bibliographic search methods

Completed and ongoing trials will be identified through searches of the following trial registries:

- ClinicalTrials.gov via https://www.clinicaltrials.gov/
- WHO International Clinical Trials Registry Platform (ICTRP) via https://www.who.int/clinical-trials-registry-platform

Additional relevant studies will be identified by:

- Screening reference lists of any reviews (systematic or non-systematic) identified by our searches
- Reviewing the reference lists of any study report included at full-text
- Hand searching the websites of the manufacturer/or licence holders for each test
- Information submitted by test manufacturers

### 3.2.3 Managing the searches

Search results will be exported to EndNote 20 for deduplication using the default deduplication settings and manual review of records. Search results will be exported to Microsoft Access for screening.

## 3.3 Review strategy

Two reviewers will independently screen titles and abstracts identified by the searches. Full copies of all reports considered potentially relevant will be obtained and two reviewers will independently assess these for inclusion. Any disagreements will be resolved by consensus or discussion with a third reviewer.

Data will be extracted using standardised data extraction forms developed in Microsoft Access or Microsoft Word depending on the quantity of data available. Data extraction forms will be piloted on a small sample of papers and adapted as necessary. Data will be extracted by one reviewer and checked in detail by a second reviewer. Any disagreements will be resolved by consensus or discussion with a third reviewer.

Data will be extracted on the following: study design (RCTs, DTA studies, NRSI, qualitative, other), objective that study addresses, funding sources (public, industry, mixed), country, setting, inclusion criteria, ADHD sub-type, test details (test, threshold), comparator or reference standard test(s), sample size and outcomes specified in inclusion criteria (section 3.1).

We will consider the PROGRESS-Plus population factors, where reported. [36] PROGRESS-Plus is an acronym that describes factors that contribute to health inequity. PROGRESS stands for: place of residence, race/ethnicity/culture/language, occupation, gender/sex, religion, education, socioeconomic status, and social capital. "Plus" stands for any additional factors considered important for the specific topic under review. We will extract the following PROGRESS-Plus factors:

- personal characteristics associated with discrimination: characteristics of relevance to the current review include age, sex, ethnicity, learning disability, neurodevelopmental disorders (including autism spectrum disorders and personality disorders), developmental trauma
- looked after children
- features of relationships e.g. exclusion from school
- time-dependent relationships e.g. instances where a person may be temporarily at disadvantage
- people in the Youth Justice System or Adult Criminal Justice System

We will extract whether each PROGRESS-Plus factor was reported at baseline (y/n), the baseline data concerning the factor as reported by the authors, and whether the study reports results data stratified by the factor. Where stratified data are reported, these will be extracted.

Dichotomous clinical effectiveness data will be extracted as number of patients with events and/or number of events and total number of patients in each treatment arm. For categorical data, we will extract details on the categories assessed, the total number of patients in each treatment arm and the number of patients in each outcome category. For continuous clinical effectiveness data we will extract means/medians together with ranges, standard deviations (SD), standard errors (SE), and/or confidence intervals (CIs) for the outcome at baseline, follow-up and for change from baseline in each treatment group. For all types of clinical effectiveness data, summary effect estimates together with 95% CIs and p-values for comparisons between groups together with details on the methods of analysis, any variables controlled for in the analysis and the test statistic will be extracted.

Accuracy data will be extracted as 2x2 tables comparing the ADHD test against the reference standard, where available. If measure of accuracy (e.g. sensitivity, specific, Receiver Operating Characteristic [ROC] plot, area under ROC cure [AUC]) are reported without providing the information needed to calculated 2x2 tables, then these data will be extracted. Data will be extracted for over test scores and for individual test sub scores,

where available. Where multiple sets of 2x2 data are reported in a single study, for example for different tests, target conditions, ADHD subtypes, thresholds, or subgroups of interest, all data will be extracted. For studies comparing two index tests and a reference standard, if full cross-classifications of test results (2x2x2 data) are reported, these will also be extracted.

Study findings will be extracted from qualitative studies as direct quotes, where appropriate.

## 3.4 Quality assessment strategy

The methodological quality of included RCTs will be assessed using the updated Cochrane Risk of Bias Tool (ROB 2.0).[37] NRSI will be assessed using the ROBINS-I tool.[38] DTA studies will be assessed for methodological quality using the most recent version of the QUADAS tool. We are currently in the process of developing QUADAS-3; if a version if ready for piloting by the time we start data extraction then this version will be used, otherwise we will use QUADAS-2.[39] Detailed guidance for reviewers on how to complete the assessments for studies included in the review will be produced prior to starting the quality assessment. Where other types of studies are included, we will use the LATITUDES Network to identify the most appropriate tool to assess these studies.[40] Quality assessment will be undertaken by one reviewer and checked by a second reviewer. Any disagreements will be resolved by consensus or discussion with a third reviewer.

## 3.5 Synthesis methods

For each of the four objectives (obj 1 to 4), a narrative summary of all of the included studies will be presented. This will include a summary of the study characteristics (e.g. study designs, sample size, geographical location, year, age group, test evaluated), outcomes reported and study quality. We will also narratively summarise baseline data for PROGRESS-Plus factors, and whether the studies report results data stratified by these factors. The synthesis will be stratified by technology evaluated, whether the tests was evaluated in isolation or in combination with clinical assessment, and on test threshold (accuracy studies only). Where data are available, subgroup analyses will be conducted to determine whether results differ according to the following subgroups:

- Age (children, young people, and adults)
- Sex
- Ethnicity
- People with mental health, behavioural and neurodevelopmental conditions

People with developmental trauma

- People in the Youth Justice System or Adult Criminal Justice System
- Looked-after children

If sufficient data are available for any reported outcome, meta-analysis will be carried out to generate summary effect estimates. For studies of effectiveness, random effects meta-analysis will be performed, allowing for heterogeneity across studies. A restricted maximum

likelihood (REML) approach will be used to estimate the between-studies heterogeneity parameter, tau. Heterogeneity and inconsistency across studies will be quantified using the tau and $I^2$ statistics.[41] Fixed effect meta-analyses will be performed as sensitivity analyses, or as the sole analyses if insufficient data are available to estimate tau. Where observational (cohort) studies are synthesised, estimates that have been adjusted for potential confounders will be used where available.

For accuracy data, coupled forest plots of sensitivity and specificity will be used to display results from individual studies, to allow visual assessment of heterogeneity. Study-level results will also be plotted in Receiver Operating Characteristic (ROC) space. Bivariate random effects meta-analyses of sensitivity and specificity will be performed, with binomial likelihoods.[42, 43] Meta-analyses stratified by diagnostic threshold will produce summary estimates of sensitivity and specificity at each threshold, with 95% confidence intervals (CIs) and 95% confidence ellipses. These summary estimates and ellipses will be added to the summary ROC plots. Additional meta-analyses including all diagnostic thresholds will be used to produce summary ROC (HSROC) curves, which will also be added to these plots. We do not anticipate having sufficient studies for formal investigation of heterogeneity.

Where studies compare the accuracy of two index tests, we will calculate comparative measures of test accuracy (e.g. differences in or ratios of sensitivity and specificity). If multiple studies make the same comparison and fully cross-classified data (2x2x2 tables of test results) are available, the model proposed by Trikalinos *et al* will be fitted to produce summary comparative measures, while allowing for both within and between study test comparisons.[44] If fully cross-classified data are not available, bivariate meta-regression with index test as a covariate will be fitted to the subset of studies making the same comparison, producing summary comparative measures.[45]

If two or more qualitative studies are identified that report data on the same outcomes, we will use the meta-aggregative approach to qualitative synthesis based on guidance from the Joanna Briggs Institute (JBI).[46] This involves extracting study findings, often as a direct quote, then creating categories of findings and, where possible, pooling the categories of findings into synthesised findings. Synthesised findings aim to convey the overall meaning of the categorised findings.

# 4 Methods for synthesising of cost effectiveness

## 4.1 Identifying and systematically reviewing published cost-effectiveness studies

We will conduct a systematic review to identify previous studies that compare the cost-effectiveness of tests that combine measures of cognition and motor activity for the assessment of ADHD with current methods of assessment based on NICE guideline (NG87).

We will search the following databases:

- MEDLINE (MEDALL) via Ovid;
- Embase via Ovid;
- NHS EED database via: https://www.crd.york.ac.uk/CRDWeb/
- INAHTA database via: https://www.inahta.org/hta-database/
- Tufts CEA Registry via: https://cear.tuftsmedicalcenter.org/

We will also include any relevant papers on cost-effectiveness identified in the clinical effectiveness reviews, search citations in relevant publications that we identify, and ask experts in the field.

We will assess the quality of the included cost-effectiveness studies using the Drummond checklist.[47]

We will run additional targeted searches to identify inputs to the economic model as required.

## 4.2 Evaluation of costs, quality of life and cost-effectiveness

A decision-analytic model will be developed to estimate the incremental costs and quality-adjusted life years (QALYs) of tests that combine measures of cognition and motor activity for the assessment of ADHD, in combination with current methods of assessment, compared to current methods of assessment alone, for each of the following purposes:

i) assisting diagnosis of ADHD in people referred with suspected ADHD (Objective 1)
ii) assisting diagnosis of ADHD in people referred with suspected ADHD for whom current assessment cannot reach a diagnosis (Objective 2)
iii) to assist in dose titration and treatment decisions in people with a diagnosis of ADHD (Objective 3)
iv) to assess treatment effectiveness for long-term treatment monitoring for people with a diagnosis of ADHD (Objective 4)

### 4.2.1 Population

We consider the following populations:

**Population 1a:** Patients suspected of having ADHD

**Population 1b:** Patients who have had an initial assessment for ADHD and where diagnosis is unclear. Population 1b is a sub-group of population 1a.

**Population 2:** Patients being treated for ADHD

If sufficient evidence is identified, subgroup analyses will be presented for:

- Age (children, young people, and adults)
- Sex
- Ethnicity
- People with mental health, behavioural and neurodevelopmental conditions People with developmental trauma
- People in the Youth Justice System or Adult Criminal Justice System
- Looked-after children

### 4.2.2 ADHD diagnosis assessment strategies

We will include tests that combine objective measures of cognition and motor activity for the assessment of ADHD that are evaluated in the assessment of clinical effectiveness (Section 3) and for which there is sufficient evidence available for the model. These may include: QbTest, QbCheck, EF Sim, EF Sim Web Version, Nesplora Kids and Nesplora adults.

Current methods for diagnosing ADHD are assessment by a healthcare professional (without use of the objective assessment methods above) using history taking, and third-party observational reports, and questionnaires (NICE guideline (NG87)).[14] These more often take place remotely for adults, and in-person for children.

We will evaluate the following diagnostic assessment strategies:
**Strategy 1:** Everyone receives standard assessment.
**Strategy 2:** Everyone receives standard assessment with a test that combines objective measures of cognition and motor activity for the assessment of ADHD
**Strategy 3:** Everyone receives standard assessment, and those patients with an unclear diagnosis receive further assessment with a test that combines objective measures of cognition and motor activity for the assessment of ADHD

For Objective 1 we will compare strategies 1 and 2 in patients suspected of having ADHD (Population 1a). For Objective 2 we will compare strategies 1 and 3 in patients who have had an initial assessment for ADHD and where diagnosis is unclear (Population 1b).

### 4.2.3 Treatment of ADHD

Patients who are diagnosed with ADHD are managed using a combination of behavioural interventions, educational support, psychosocial support, lifestyle and self-care, awareness and education, and medication, as described in section 1.2.3. Medications including stimulants (e.g., methylphenidate or amphetamine-based drugs) and non-stimulants (e.g., atomoxetine, guanfacine, clonidine), may be prescribed based on the severity of symptoms and individual response.[25]

For those patients where pharmacological treatment is indicated, medication should be initiated following behavioural interventions. Patients will then undergo a "dose titration" period during which they begin with a low-dose of first line treatment (usually methylphenidate), and then are assessed at 2-week intervals for efficacy and side-effects where decisions to change the dose or treatment are made. The choice of treatments will be based on individual circumstances, including accounting for adherence to medication. The period of time before the treatment and dose are settled upon varies greatly across patients. Currently, the assessments are made clinically, but objective tests may have a role in assisting assessment during the dose-titration period (Objective 3).

Following the dose titration period, patients are monitored regularly (annually for adults and at least every 6-months for children), including an assessment of whether medication needs to be adjusted, which is based upon clinical assessment of efficacy and side-effects and uses information from questionnaires compared to baseline measures. Patients may also take a "drug holiday", to see if they still need to take medication (our clinical advisors consider this every 3-5 years for adults), and at this point patients may either stop treatment or re-start or adjust treatment. Objective tests may have a role in assisting treatment decisions in long-term management of patients (Objective 4).

We will evaluate the following diagnostic assessment strategies:
**Strategy 4:** Standard assessment for dose titration
**Strategy 5:** Standard assessment with a test that combines objective measures of cognition and motor activity for the assessment of ADHD for dose titration
**Strategy 6:** Standard assessment for monitoring
**Strategy 7:** Standard assessment with a test that combines objective measures of cognition and motor activity for the assessment of ADHD for monitoring

For Objective 3 we will compare strategies 4 and 5 in patients being treated for ADHD where pharmacological treatment is indicated (Population 2). For Objective 4 we will compare strategies 6 and 7 in patients being treated for ADHD (Population 2) following the dose-titration period.

### 4.2.4 Model structure

In this section for brevity we use the term "objective test" to indicate a test that combines objective measures of cognition and motor activity for the assessment of ADHD.

The model structure will be developed to capture the short- and long-term costs and benefits of objective measures of cognition and motor activity for the assessment of ADHD, and will be informed by the findings of our review of clinical and cost-effectiveness studies and discussions with our clinical advisors and expert committee members.

A draft model structure is provided in Appendix 2. We envisage that there will be a short-term part of the model (Figure 1, Appendix 2) with a decision-tree structure to capture the

process of diagnosis of ADHD. For Objective 1, patients (Population 1a) begin waiting for an assessment (following triage for suspected ADHD) and then will have an initial assessment for ADHD either with (Strategy 2) or without (Strategy 1) using an objective test. Following this, there will be a proportion of patients for whom the diagnosis is clear, and a proportion where the diagnosis is unclear, which may be different between Strategy 1 and 2. For those with an unclear assessment under Strategies 1 and 2, further assessments will be undertaken before a diagnosis is made. Patients who receive a diagnosis of ADHD will including those with ADHD (true positives) and those without (false positives). Patients who do not receive a diagnosis of ADHD include those with ADHD (false negatives) and those without ADHD (true negatives). The accuracy of the diagnosis will depend on whether the patient had a clear or unclear diagnosis. Those with a diagnosis of ADHD (population 2) then enter the long-term treatment part of the model (Figure 2, Appendix 2).

For Objective 2, we consider patients for whom diagnosis was unclear after initial assessment with Strategy 1 (population 1b patients). For these patients there will be further assessment either with (Strategy 3) or without (Strategy 1) using an objective test, following which a diagnosis is made. Under strategy 3 we assume that there may be a proportion of patients whose diagnosis becomes clear after using the objective test. As for Objective 1, the accuracy of the diagnosis will depend on whether the patient had a clear or unclear diagnosis. Those with a diagnosis of ADHD (population 2) then enter the long-term treatment part of the model (Figure 2, Appendix 2).

In the long-term treatment part of the draft model (Figure 2, Appendix 2) we assume that the main use of objective tests will be to assist with dose-titration and treatment decisions, and for reviewing treatment in long-term monitoring appointments. The long-term treatment model begins with an initial dose-titration period with assessments every 2 weeks until a treatment and dose is settled where the assessments either do (Strategy 5) or do not (Strategy 4) use an objective test. Once treatment is settled patients receive regular monitoring (annually for adults, and every 6 months for children) where their treatment may be adjusted. This is modelled with a Markov model structure (Figure 2, Appendix 2) with tunnel states and includes a treatment holiday every 3 years following which patients may stop treatment, or continue/adjust treatment and cycle back to routine monitoring. The routine assessments may include an objective test (Strategy 7) or not (Strategy 6).

For Objective 3 we will compare strategies 4 and 5 in patients being treated for ADHD where pharmacological treatment is indicated (Population 2) using the long-term treatment model from the initial dose-titration state. For Objective 4 we will compare strategies 6 and 7 in Population 2 following the dose-titration period by starting the model from the end of the dose-titration state.

An NHS and personal social services (PSS) perspective will be taken with a life-time horizon where costs and QALYs are discounted at an annual rate of 3.5%. The model will include all

relevant health effects, including patients and other relevant people (such as carers), where evidence can be identified.

Probabilistic sensitivity analysis where parameter uncertainty is captured with probability distributions and simulation will be used to estimate incremental cost-effectiveness ratios and expected net benefits at commonly used NICE willingness to pay thresholds. Uncertainty will be presented using cost-effectiveness planes and cost-effectiveness acceptability frontiers. One way sensitivity analyses will be performed for all key model parameters.

### 4.2.5 Model inputs

Model inputs will be derived from the clinical and cost-effectiveness reviews where possible, supplemented by targeted literature searches. Where there is insufficient evidence available we will base parameters on expert opinion and conduct scenario analyses to explore the impact of these assumptions on the results.

### 4.2.6 Scenario analyses

Scenario analyses will be conducted to explore the sensitivity of results to key model assumptions.

### 4.2.7 Health outcomes

The model will include the impact of the different assessment strategies for ADHD and subsequent treatment on health-related quality of life (HRQoL). The model will include the HRQoL impact of adverse events for those on pharmacological treatment, including those who do not have ADHD but are treated following a false positive diagnosis. The lost benefits in terms of HRQoL for those who have ADHD but are not treated, due to being on a waiting list for assessment, and for those who are not diagnosed (false negatives). The impact on carers will be included in the model if evidence is available, and will be discussed if no evidence is identified.

### 4.2.8 Costs

Costs will be considered from an NHS and Personal Social Services perspective. Costs will be obtained from routine NHS sources (NHS reference costs, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF)), our reviews of previous cost-effectiveness models, targeted literature searches, and through discussions with the manufacturers and clinical advisors. It has been suggested that the potential benefit of tests that combine objective measures of cognition and motor activity for the assessment of ADHD relate to a more efficient diagnosis requiring fewer consultations (MIB318). We therefore include costs of the number and length of appointments for diagnosis, dose-titration and long-term management.

We will include the following costs:

- Costs related to using the technologies (including device, hardware and software, and time required to conduct the test and analyse results)
- Cost of training staff to operate the technology and interpret results
- Costs of resources associated with assessing patients whilst diagnosing ADHD, including the number and length of clinical appointments prior to a diagnostic decision
- Costs of resources associated with the dose-titration period for patients diagnosed with ADHD for whom pharmacological treatment is indicated, including the number and length of clinical appointments
- Treatment costs
- Cost of management of adverse events
- Costs of resources associated with long-term management of patients diagnosed with ADHD for whom pharmacological treatment is indicated, including the number and length of clinical appointments

We will not include costs that are incurred regardless of assessment strategy taken for a given objective.

# 5 Handling information from the companies

All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than 15 February 2024. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any 'commercial in confidence' data provided by manufacturers, and specified as such, will be highlighted in blue and underlined in the assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted. If confidential information is included in economic models then a version using dummy data or publicly available data in place of confidential data will be provided.

# 6 Competing interests of authors

None of the authors have any competing interests.

# 7 Timetable/milestones

| Milestone | Date to be completed |
|---|---|
| Draft protocol | 2 November 2023 |
| Final protocol | 14 November 2023 |
| Progress report | 15 February 2024 |
| Draft assessment report | 15 April 2024 |
| Final assessment report | 14 May 2024 |

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## Appendix 1: Literature searches

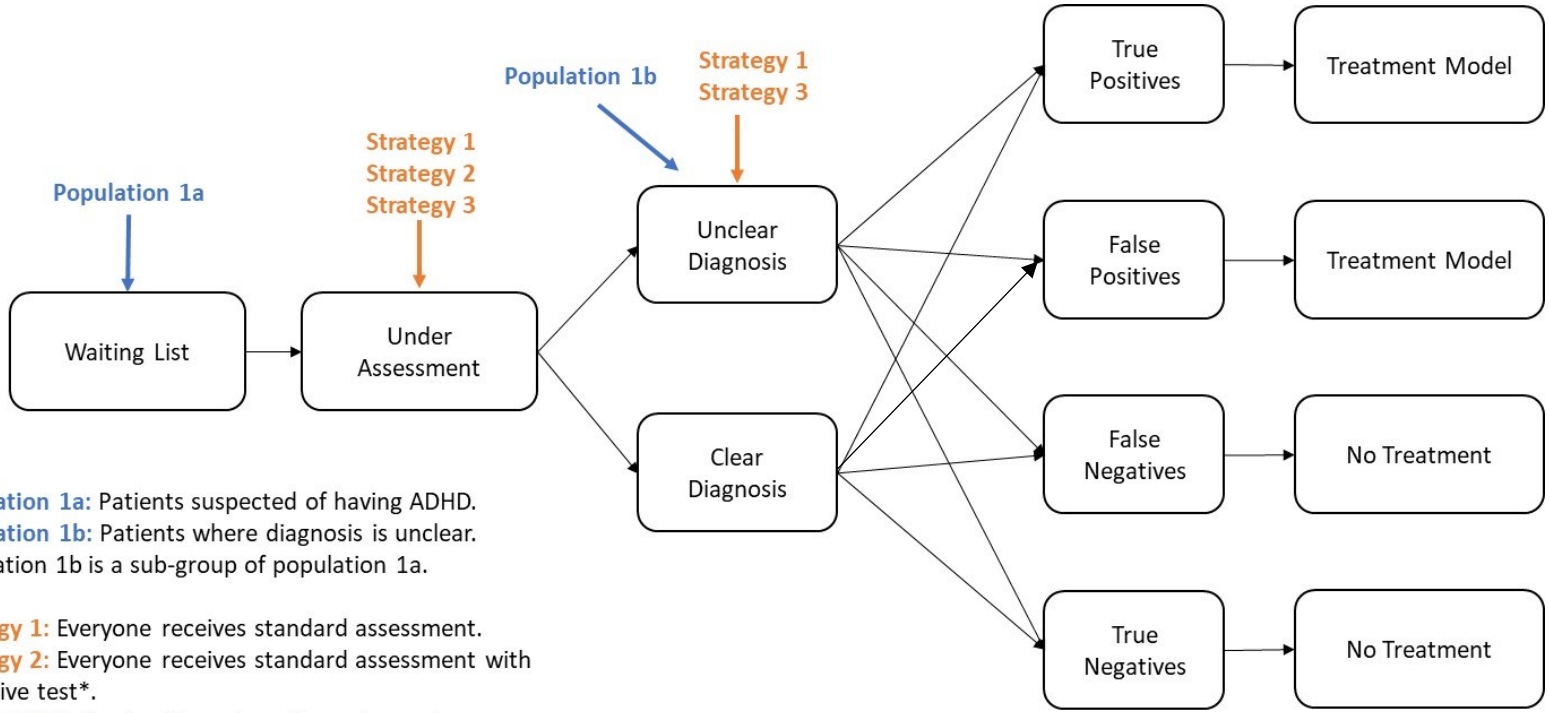
Search purpose: to identify studies reporting data on the clinical or cost effectiveness, accuracy, or the technical performance, of the technologies specified in the scope.

Database: MEDLINE (MEDALL)
Host: Ovid
Data parameters: 1946 to present
Date of search: 6 November 2023

1 (QbTest* or "Qb Test*" or "(Qb) Test*" or "Qb Mini*" or "QbMini*" or (("Quantified Behavior*" or "Quantified Behaviour*") adj5 test*) or QbTech).af. (68)
2 (QbCheck* or "Qb Check*" or "(Qb) Check*").af. (1)
3 (Nesplora* or "Giunti psychometrics").af. (21)
3 (ARVO* or EFSim* or "EF Sim*" or EPELI or "Peili Vision Company").af. (1501)
4 Attention Deficit Disorder with Hyperactivity/ or ADHD.af. (44375)
5 4 and 5 (5)
6 ((motion* adj5 senso*) and (hyperactivity or ADHD)).ti,ab,kf. (6)
7 1 or 2 or 5 or 6 (99)
8 NCT03368573.af. or (QUOTA and adhd).ti,kf. [QB test] (3)
9 NCT02209116.af. or ((AQUA and ADHD) or AQUA2).ti,kf. [QB test] (5)
10 NCT02473185.af. [QB test] (1)
11 NCT02477280.af. [QB test] (0)
12 NCT05846815.af. [ARVO Test] (0)
13 9 or 10 or 11 or 12 or 13 (9)
14 8 or 14 (100)

# Appendix 2: Draft Model Structure

**Figure 1 Draft structure for the short-term diagnosis model**



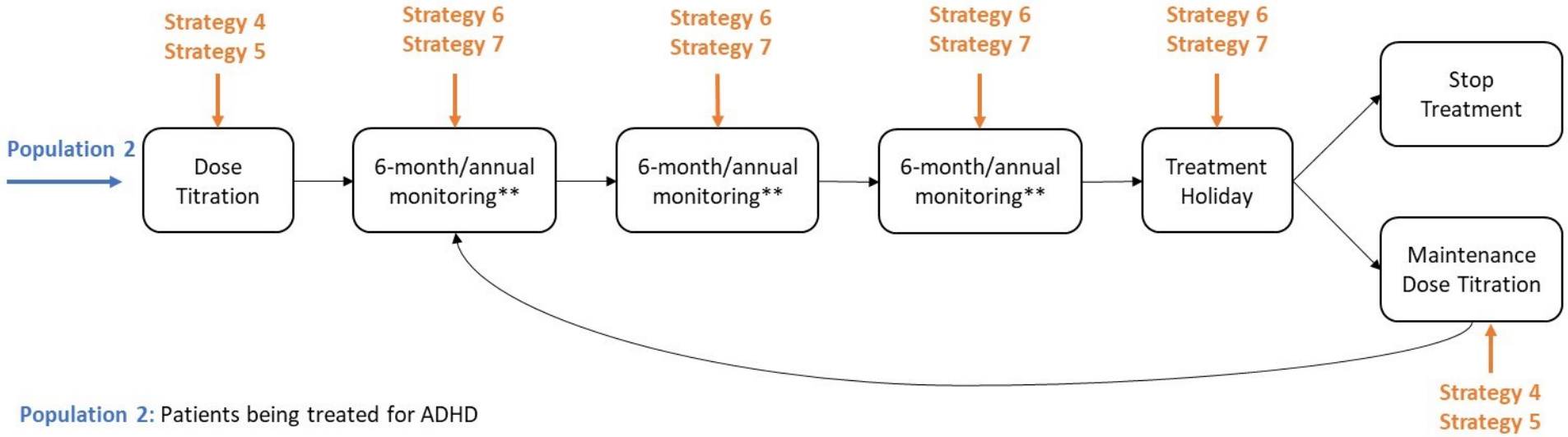

**Population 1a:** Patients suspected of having ADHD.
**Population 1b:** Patients where diagnosis is unclear.
Population 1b is a sub-group of population 1a.

**Strategy 1:** Everyone receives standard assessment.
**Strategy 2:** Everyone receives standard assessment with objective test*.
**Strategy 3:** Patients with a clear diagnosis receive standard assessment. Patients with an unclear diagnosis receive standard assessment with objective test*.

*Objective test refers to a test technology that combines measures of attention and motor activity for the assessment of ADHD.

**Objective 1 compares strategies 1 and 2 in population 1a.**
**Objective 2 compares strategies 1 and 3 in population 1b.**

**Figure 2 Draft structure for the long-term treatment model for patients diagnosed with ADHD**




**Population 2:** Patients being treated for ADHD

**Strategy 4:** Standard assessment for dose titration.
**Strategy 5:** Standard assessment with objective test* for dose titration
**Strategy 6:** Standard assessment for monitoring
**Strategy 7:** Standard assessment with objective test* for monitoring

*Objective test refers to a test technology that that combines measures of attention and motor activity for the assessment of ADHD.
**Monitoring review cycles are 6-months in children and annual in adults.

**Objective 3 compares strategies 4 and 5 in population 2**
**Objective 4 compares strategies 6 and 7 in population 2.**