NIHR Reference No. DAP61

Final amended version, 17/02/22

Assessment Group's Protocol
Devices for remote continuous monitoring of people with Parkinson's disease: a systematic review and economic analysis

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Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined, all depersonalised data (DPD) are highlighted in pink and underlined.

PROSPERO registration number: CRD42022308597.

Plain English Summary

Parkinson's disease is a condition that affects the brain, resulting in a progressive loss of coordination and movement problems. In the early stages of Parkinson's disease, the 3 main symptoms are shaking (tremor), slowness of movement (bradykinesia) and muscle stiffness (rigidity). Other physical symptoms that can occur during the early stages of the disease include balance problems, nerve pain and sleep disturbance. People with advanced Parkinson's disease may have more complex symptoms including anxiety, depression and dementia. Advanced Parkinson's disease has a severe impact on the quality of life of patients, their families and carers. About 10% of patients have advanced disease.

The drug levodopa is used to manage motor symptoms, but it may cause motor complications, including fluctuation in response and involuntary limb movement (dyskinesia). Response fluctuations are characterised by large variations in motor performance, with normal function during the 'on' period, and weakness and restricted mobility during the 'off' period. 'Wearing off' of the drug or 'End-of-dose' deterioration with progressively shorter duration of benefit can also occur over time. Treatment can also cause side-effects such as impulse control disorders (e.g. compulsive gambling, hypersexuality, binge eating and obsessive shopping), excessive sleepiness or sudden onset of sleep and psychotic symptoms such as hallucinations and delusions.

Remote monitoring devices could potentially be used to continuously measure the motor symptoms of Parkinson's disease. They are intended to be used alongside subjective judgement in consultations between the patient and clinician to improve the management of symptoms. Remote monitoring devices include the Personal KinetiGraph (PKG) Movement Recording System (Global Kinetics), Kinesia 360 and KinesiaU (Great Lakes Neurotechnologies), PDMonitor (PD Neurotechnology) and STAT-ON (Sense4Care).

The purpose of this project is to investigate the evidence on the potential clinical and economic value of all these remote monitoring devices, alongside clinician judgement, for monitoring motor and non-motor symptoms in people with Parkinson's disease. To achieve this, we will search for all relevant published studies on PKG, Kinesia 360, KinesiaU, PDMonitor and STAT-ON and analyse the reported data to determine whether these technologies provide clinical benefits. If data permits, an economic analysis will be conducted to investigate whether using these devices represent value for money in the NHS.

1 DECISION PROBLEM

1.1 Purpose of the decision to be made

The purpose of this assessment is to investigate the use of remote monitoring devices for people with Parkinson's disease. The assessment will consider the use of devices that continuously monitor motor symptoms, tremors and sleep disturbance, alongside clinical judgement, and their potential impact on treatment management and disease symptoms. The assessment will consider existing evidence (and identify potential evidence gaps) on whether PKG, Kinesia 360, KinesiaU, PDMonitor and STAT-ON have the potential to be clinically useful and cost-effective additions to current monitoring strategies.

1.2 Interventions

This assessment will evaluate whether remote continuous monitoring devices are effective and reliable for monitoring motor symptoms, tremors and sleep disturbance in people with Parkinson's disease. They could potentially be used alongside clinical judgement to help manage symptoms at:

- all review appointments
- a subset of review appointments (for example, if motor fluctuations are not being adequately managed)
- between review appointments (to allow for more frequent monitoring of symptoms, or where there is substantial time between appointments)
- in place of in-person review (including remote management, remote appointments, and where a patient might be unable to attend in person).

This assessment will consider only wearable remote monitoring devices that produce results with no input, or limited input, from the user. All technologies assess, at least, bradykinesia and dyskinesia. Five relevant remote monitoring devices with CE marks (or in the process of seeking CE-marking) have been identified for consideration:

- Personal KinetiGraph (PKG) Movement Recording System (Global Kinetics),
- Kinesia 360 (Great Lakes Neurotechnologies)
- KinesiaU (Great Lakes Neurotechnologies)
- PDMonitor (PD Neurotechnology)
- STAT-ON (Sense4Care).

Assessing movement at night may help identify sleep related issues such as sleep fragmentation (interrupted sleep), which could be caused by symptoms returning when medications wear off or nocturia (night time urination).

Clinical experts highlighted that the technologies may not be suitable for people with severe cognitive impairment, Alzheimer's disease or people with impulse disorders, as they can require user input to measure medical compliance, so may cause stress and anxiety in these patients, unless a carer can assist with this. The value of the technologies may be limited in people who are extremely frail or whose symptoms are mostly restricted to their lower limbs (for wrist-worn devices).

Clinical experts stated that there may be increased administration time associated with ordering the technologies and navigating internal IT systems; the ease with which data generated by the technologies could be integrated into existing patient data systems could be a barrier to implementation.

1.2.1 Personal KinetiGraph (PKG) Movement Recording System (Global Kinetics)

The Personal KinetiGraph (PKG) Movement Recording System (Global Kinetics) is a Class IIa CE marked system that uses a PKG Watch that continuously measures movement, over a period of 6 days. It is intended to quantify kinematics of movement disorder symptoms in conditions such as Parkinson's disease, including tremor, bradykinesia (slowness) and dyskinesia (involuntary movements). It has event markers for medication reminders and patient acknowledgement. It is also intended to be used to monitor activity associated with movement during sleep. The company state that PKG is an adjunct to clinical practice and should be used in combination with patient and healthcare consultation. They envisage that the PKG is used twice a year, although there is some uncertainty about the best time to use the PKG; varying between every six months regardless of current symptoms to only when there is a suspicion that medication is not adequately controlling symptoms.

Healthcare professionals can order the PKG online. The company then sends the watch directly to the person who will wear it (for a period of 6 days), also providing a paid, addressed envelope for the watch to be returned to the company. Data is then extracted and processed by cloud-based algorithms and a report is then generated for the healthcare professional to view online.

The PKG measures bradykinesia, dyskinesia, tremors, motor fluctuations, immobility and when the watch is not being worn. It can also prompt the user to take their medication at prescribed times and the user can register when they have taken their medication. As well as providing the raw data, it can generate a report based on movement over a 6-day period using validated proprietary algorithms. The report includes summary graphs showing measurements over time and the summary following results, along with a suggested target range or interpretation:

- A bradykinesia score
- A dyskinesia score

- A fluctuation dyskinesia score
- Percentage of time with tremor
- Percentage of time immobile (indicative of daytime sleepiness).

The company has stated that new versions of the technology will include 24-hour measurements of sleep-related functions. The device is intended to be interpreted only by trained technicians or clinicians, and as an aid to existing clinical methods. It is not intended to be the sole or primary means of clinical assessment. The company does not recommend use of the technology for patients who have restricted movement (for example, confined to bed) or for patients who operate heavy machinery for prolonged periods.

The company provides healthcare professionals with education and training, and state that healthcare professionals should complete an average of 15 to 20 PKGs to be proficient, supported by an eLearning module, which takes approximately 1 to 2 hours.

1.2.2 Kinesia 360 (Great Lakes Neurotechnologies)

The Kinesia 360 (Great Lakes Neurotechnologies) is a Class I CE-marked system that monitors physical motion and muscle activity to quantify movement disorder symptoms and assess activity. The Kinesia 360 system consists of a tablet, sensors and charge pad, USB cable and charge pad power cable. Sensors worn on the wrist and ankle combined with a mobile application continuously record data, including dyskinesia and tremor. The sensors record data all day and recharge overnight for extended home use. The mobile application also includes electronic diaries for capturing patient-reported outcomes and customizable medication diaries.

When the Kinesia Sensor bands are returned to the charging pad, data from the motion sensors is automatically downloaded and then uploaded to the Kinesia Web Portal and algorithms are used to detect symptoms and calculate severity scores. Clinicians can view web-based reports that include:

- A dyskinesia score
- Total and percentage of time with tremor
- Total and percentage of time at rest
- Total and percentage of active time (but not walking)
- Number of steps
- A symptom summary report that displays how tremor, slowness, dyskinesia and walking change over time
- A dose report that shows how tremor, slowness, dyskinesia and walking change as a function of different medication or therapy doses.

1.2.3 KinesiaU (Great Lakes Neurotechnologies)

The KinesiaU (Great Lakes Neurotechnologies) measures tremor, slowness and dyskinesia using a smartwatch and smartphone application. Patients can view reports in real-time and share these with their healthcare professionals. The product is to be used only under the direction of a qualified clinician and all changes to therapy regimens are to be based solely on the clinical judgement of the clinician. The company is seeking CE-marking.

The reports rate the severity of tremor, slowness and dyskinesia symptoms into good, mild, moderate and severe categories. This can be measured through specific active tasks or through continuous recording. To start a continuous (all day) recording, the user must tap the 'Continuous' button on the home screen. The smartwatch application must be kept open during the recording. Active tasks may be performed during the continuous recording.

Reports can be produced throughout the day and over the course of days, weeks and months in response to therapy and activities. The report page on the smartwatch application displays the severity of the selected symptom (tremor, slowness and dyskinesia) averaged for the selected time range. The symptoms can be displayed individually or averaged together and shown as 'All symptoms'. The mobile application also includes customizable medication and exercise diaries, which can be added to the report. Patients can view reports in real-time and share reports (pdf format) with their healthcare professionals.

1.2.4 PDMonitor (PD Neurotechnology)

The PDMonitor system (PD Neurotechnology) is a Class IIa CE-marked system that measures activity/posture, bradykinesia, freezing of gait, gait disturbances, wrist tremor, leg tremor, dyskinesia and 'on' and 'off' periods. The duration and frequency of use is decided by the physician. The device should be removed when performing intense fitness activities.

The PDMonitor system consists of the SmartBox, 5 monitoring devices and a PDMonitor mobile application. The devices are worn on both wrists, both ankles and one is worn on the waist, and acquire movement data for assessing motor symptoms. The PDMonitor SmartBox is a docking station for charging the monitoring devices, collecting, storing and processing data and uploading them to the PD Neurotechnology storage service. The SmartBox must be connected to the PD Neurotechnology storage service to be properly configured, either via an ethernet cable or an available Wi-Fi network; this requires an internet connection. A web-based application can be used by healthcare professionals to view and download patient reports. The PDMonitor mobile application is an electronic diary for medications, diet and symptoms related to Parkinson's disease. It also provides a summary of daily activity as recorded by the PDMonitor system.

1.2.5 STAT-ON (Sense4Care)

The STAT-ON (Sense4Care) is a Class IIa CE-marked, waist-worn inertial recorder, configured by a doctor and used by the patient in clinical, ambulatory or home environments. It measures motor disorders and events when worn by someone with Parkinson's disease, but does not measure tremor. The device measures dyskinesia, 'on' and 'off' periods, gait parameters (including bradykinesia and freezing of gait), falls, energy expenditure and posture. It can also register when medication has been taken and up to 10 alarms per day can be set.

Health professionals should manage use of the device; they should provide the sensor to the user correctly configured and charged. Results can be used to adjust or evaluate a therapy or to adjust a person's diet.

The STAT-ON system consists of a monitoring device, its base charger, a belt and a mobile application. The device collects data and uses artificial intelligence algorithms to process it. Results are stored in its internal memory. The smartphone application connects to the STAT-ON device via Bluetooth. The mobile application is used for configuring the system and for downloading the data. It also sends the data as a report by email.

The company has advised that the STAT-ON could be worn during the night to monitor movement. The user should wear the device for a minimum of 5 days (ideally for 7 days), totalling a minimum of 24 hours over the 5 days to generate sufficient data. After this, a report can be generated at any time. A health professional can download the report to their phone using the STAT-ON application which automatically generates a report of the motor state and symptoms during time of use. Reports include a summary of activity and prevalence of symptoms during the monitored period, including:

- Total freezing of gait episodes and average number of episodes per day
- Average minutes walking and number of steps per day
- Number of falls
- Time in 'Off'/Intermediate/'On'
- Time with dyskinesias.

As well as numerically, data is also presented in graphs. In addition to a summary report, a more detailed report with further data analysis can also be produced.

The STAT-ON device is not indicated for children or for people with Parkinson's disease with Hoehn & Yahr Scale 5. The device should not be worn by a person in a wheelchair or using crutches as the results will not be valid.

1.3 Populations and relevant subgroups

The population of interest is people with Parkinson's disease.

The subgroups relevant to this appraisal will be:

- Patients grouped according to disease stage (e.g. early, maintenance or late-stage), current treatment and treatment options
- People with advanced Parkinson's disease (however defined, but including patients receiving deep brain stimulation, levodopa-carbidopa intestinal gel or apomorphine)
- People with communication barriers, which limit ability to describe their symptoms
- According to ethnicity.

1.4 Place of the intervention in the treatment pathway

1.4.1 Parkinson's disease

Parkinson's disease is a condition that affects the brain, resulting in a progressive loss of coordination and movement problems. It is caused by a loss of cells in the brain that are responsible for producing dopamine, which helps to control and coordinate body movements. In the early stages of Parkinson's disease, the 3 main symptoms are shaking (tremor), slowness of movement (bradykinesia) and muscle stiffness (rigidity). These develop gradually, in no particular order.[1] Other physical symptoms that can occur early on include balance problems, nerve pain and sleep disturbances. There is no consistently reliable test that can distinguish Parkinson's disease from other conditions that have similar clinical presentations; diagnosis is primarily based on history and clinical examination.[2]

Healthcare professionals often refer to different 'stages' of Parkinson's disease.[3] The early or diagnosis stage describes the period when someone is first experiencing symptoms, being diagnosed and coming to terms with this. The maintenance stage is when symptoms are controlled, perhaps by medication. Advanced Parkinson's disease is defined by the presence of more complex symptoms that significantly impact daily living, including anxiety, depression and dementia. Advanced Parkinson's disease has a severe negative impact on the quality of life of patients, their families and carers. The palliative stage involves providing relief from the symptoms, stress and pain of the condition.[3]

The Parkinson's UK report on the incidence and prevalence of Parkinson's disease states there are around 145,500 people living with Parkinson's disease in the UK.[4] Men are more likely to develop Parkinson's disease than women, and the risk of developing the disease increases sharply with age. It is estimated that around 10% of patients have advanced disease.[5] In 2018 there were 6,505 deaths due to Parkinson's disease in England and Wales. All deaths occurred in people aged 50 or above, with 87% occurring in people aged 75 years or above.[5]

1.4.2 Treatment for Parkinson's disease

Recommendations for the treatment of Parkinson's disease are given in the NICE guideline for Parkinson's disease in adults (NG71).[2] Patients should be offered both non-pharmacological and pharmacological management for motor symptoms. This includes referral to a physiotherapist for physical activity regimes. This can also include referral to an occupational therapist for people with difficulties doing day-to-day activities.

1.4.2.1 Pharmacological treatment

Levodopa is the most commonly prescribed treatment for managing the motor symptoms of Parkinson's disease in the early stages.[2] However, it may be associated with significant motor complications, including response fluctuations and dyskinesias (involuntary movements), particularly after long-term use. Response fluctuations are characterised by large variations in motor performance, with normal function during the 'on' period, and weakness and restricted mobility during the 'off' period. 'Wearing off' of the drug or 'End-of-dose' deterioration with progressively shorter duration of benefit can also occur over time. Sleep disturbances such as insomnia, nocturia (night time urination) and restless leg syndrome ('jumping' of the legs and/or arms) can be caused by 'wearing-off' periods during the night. Dopaminergic therapies can also cause non-motor adverse effects such as impulse control disorders, excessive sleepiness or sudden onset of sleep and psychotic symptoms such as hallucinations and delusions. Patient preferences are key to treatment decisions; the benefits of treatment must be balanced against the potential side-effects.

Dopamine agonists, monoamine oxidase Type B (MAO-B) inhibitors or catechol O methyl transferase (COMT) inhibitors are offered as additional treatment for people who have developed dyskinesia or motor fluctuations despite optimal levodopa therapy. If the dyskinesia remains uncontrolled, amantadine can be considered.

The NICE guideline for Parkinson's disease in adults recommends adjusting medicines to reduce the occurrence of daytime sleepiness or sudden onset of sleep, having first sought advice from a healthcare professional with specialist expertise in Parkinson's disease. Modafinil should be considered to treat excessive daytime sleepiness if a detailed sleep history has excluded reversible pharmacological and physical causes. Clonazepam or melatonin may be considered to treat rapid eye movement sleep behaviour disorder if a medicines review has addressed possible pharmacological causes.[2]

1.4.2.2 Advanced Parkinson's disease

The symptoms of advanced Parkinson's disease may still be responsive to adjustments in the dose and combination of levodopa with adjuvant MAO-B and/or COMT therapies.[6] Intermittent apomorphine injection and/or continuous apomorphine infusion may also be considered for people with advanced

Parkinson's disease. Deep brain stimulation (DBS) can be considered in people with late-stage Parkinson's disease whose symptoms do not respond adequately to best medical therapy. Clinical experts highlighted that this procedure is only normally considered for people who have been taking medication for Parkinson's disease for over 5 years.

Levodopa–carbidopa intestinal gel is currently available through an NHS England clinical commissioning policy. It can be considered in certain people with advanced levodopa-responsive Parkinson's disease, with severe motor fluctuations that have not responded to available medications. NICE recommends that this policy is reviewed in light of NG71 (NICE guidelines for Parkinson's disease in adults, Section 1.8.4).[2]

1.4.3 Current monitoring strategies

Clinicians often aim to keep the dose of levodopa as low as possible to maintain good function and reduce the development of motor complications. As the disease progresses changes in treatment are usually required.[2] Therefore, it is important to regularly monitor people with Parkinson's disease to assess disease progression and adverse effects of treatment. NICE recommends that people with Parkinson's disease should be seen by a specialist every 6 to 12 months initially, then more often with increasing disease complexity, although this is often difficult because of the increasingly ageing population and demands on Parkinson's disease services.[7]

The assessment of disease symptoms, including motor symptoms, in current clinical practice varies. It includes patient or carer-reported history taking, for example diaries, and use of rating scales; in NHS practice the Movement Disorders Society (MDS) Unified Parkinson's Disease Rating Scale (UDPRS) – part 2, the Modified Bradykinesia Rating Scale (MBRS) and the Hoehn and Yahr scale are the most frequently used. Exact methodology and choice of rating scales may vary substantially between centres. Technologies such as mobile activity trackers and mobile applications may also be used to support information recorded in personal diaries, but these technologies do not appear to be in widespread use. Sleep diaries are also used.

1.4.4 Role of remote monitoring devices

People with Parkinson's disease experience a range of motor symptoms, which can fluctuate in severity during the day and between days. Remote monitoring devices are intended to be used alongside clinical judgement to assess disease severity and help manage Parkinson's disease symptoms and adverse effects of treatment. They can be used in any setting, and are most likely to be used in people's homes.

Results of the monitoring are analysed remotely, and a summary provided to the specialist physician and/or to the patient. The specialist should use this summary to assess motor symptoms (bradykinesia

and dyskinesia) and other symptoms including sleep disturbance and tremors, and how these are influenced by the use and timing of treatment. The data should be used to determine whether any changes in treatment regimen are desirable, in consultation with the patient. Results of the monitoring devices are intended to complement existing methods of assessment, such as patient-reported symptoms and clinical assessment, and are not intended to replace them.

Results from the monitoring devices may also have more general benefits, alongside leading to treatment modification. These include providing a clear and objective measurement of symptoms, which may enable both patient and clinician to better understand the patient's condition, and provide clearer justification of the value of treatment, and the need for modification. These devices may also be of particular use for patients who may have difficulty communicating, recalling or recording their symptoms; for example, due to learning difficulties or language barriers.

There is some uncertainty about when and how often remote monitoring devices might be used. PKG is suggested for use every 6 months. However, it might be used only before in-person clinic visits (which may be less frequent), or only when it might provide additional useful information; for example, if symptoms are not being successfully controlled. Conversely, it may be possible to use these devices to enable remote consultation with patients, either by replacing some in-person visits, or acting as additional consultations between in-person visits. Remote monitoring may be particularly useful for patients who may have difficulty attending in-person consultations, due to living in a remote location or having a physical disability. However, contact with healthcare professionals would still be needed for some assessments, for example to take blood pressure readings, assess cognition and to perform mood assessments.

1.5 Relevant comparators

The comparator is clinical judgement of symptoms and need for treatment modification, without the use of remote monitoring devices. This includes specialist clinical judgement, supported by history taking, patient reported diaries and use of rating scales such as the UDPRS, MBRS and the Hoehn and Yahr scales.

1.6 Key outcomes to be addressed

Outcomes to be considered fall into four key areas: the association between monitoring results and clinical measures (such as bradykinesia and dyskinesia); the intermediate impact of monitoring on treatment decisions and management; impact on clinical symptoms and disease severity; benefits and value to patients, carers and health professionals.

Costs to be considered include those associated with the use of the remote monitoring devices (e.g. acquisition and operational costs), costs of clinical management of Parkinson's disease, (including

treatment costs and healthcare utilisation e.g. review appointments), costs of hospitalisation, further tests and treatment-related adverse events. Costs will be considered from an NHS and Personal Social Services perspective.

Specific outcomes are as follows:

1.6.1 Association outcomes

Association between outputs of remote monitoring (such as bradykinesia score, dyskinesia score, sleep disturbance and tremor measures) and clinical measures, including:

- Rating scales such as the UDPRS, MBRS and the Hoehn and Yahr scales
- Other measures of bradykinesia and dyskinesia, sleep disturbance or tremor
- Clinical assessment
- Patient reported symptoms.

Any measure of association will be considered, including: sensitivity and specificity, measure of correlation, or results of regression models.

1.6.2 Intermediate impact of monitoring

All impacts on clinical decision-making:

- Changes in therapy (e.g. starting levodopa)
- Modification of current therapy dose or timing (primarily levodopa, and including potential changes to therapy identified which were contraindicated or declined by the patient)
- Use of additional interventions (including pharmacological and non-pharmacological interventions for management of motor and non-motor symptoms associated with Parkinson's disease)
- Adherence to medication
- Number and length of clinical appointments
- Incidence of remote appointments
- Ease of use/acceptability by clinicians.

1.6.3 Clinical outcomes

Measurable clinical impact of using the technologies:

- Change in clinical symptoms

- On/Off periods
- UPDRS, MBRS, Hoehn and Yahr scores
- Dyskinesia and bradykinesia scores
- Sleep disturbance
- Tremors
- Number and length of hospital admissions
- Other morbidities (including falls, hip fracture, cognitive functioning, other non-motor outcomes, adverse effects of treatment)
- Mortality.

1.6.4 Patient- and carer-reported outcomes

- Health-related quality of life
- Ease of use and acceptability for patients and carers
- Patient and carer experience (including quality of care, patient and carer satisfaction and engagement, for example, impact on discussions about symptom management, communication and relationship between patients and clinicians).

It is expected that data will not be available for many of these outcomes. They are listed here to present a complete list of outcomes of interest.

1.6.5 Costs

- Costs for consideration may include:
- Costs related to using the intervention (including any time analysing and storing data, communicating results and arranging for use of the technology)
- Cost of staff training
- Cost of review appointments
- Cost of further tests
- Cost of treatment (including costs of any adverse events).

1.7 Objectives

The aim of the project is to determine the clinical and cost-effectiveness of remote monitoring devices that continuously monitor motor symptoms, tremors and sleep disturbance, alongside clinical judgement in people with Parkinson's disease, specifically the five technologies described in Section 1.2. To achieve this, the following objectives are proposed:

Clinical effectiveness

- To perform a systematic review and, if feasible, a meta-analysis of the association between the output of the five remote monitoring devices and key indicators of disease symptoms and severity.
- To perform a systematic review, narrative synthesis and, if feasible, a meta-analysis of the clinical impact of the remote monitoring devices and, in particular, consider their impact on change in treatment strategy and on disease severity.
- To perform a systematic review and narrative synthesis of patient and physician opinions on the value and ease-of-use of the remote monitoring devices.

Cost effectiveness

- To perform a systematic review of published cost-effectiveness studies of the use of the five remote monitoring devices in the management of people with Parkinson's disease.
- To develop a decision-analytic model to estimate the cost-effectiveness of the five remote monitoring devices as an adjunct to clinical judgement for the assessment of motor and non-motor symptoms in people with Parkinson's disease compared to clinical judgement alone. If it is not feasible to estimate the cost-effectiveness for some of the devices due to a lack of comparative effectiveness evidence, the range of costs and resource consequences and potential clinical benefits associated with these devices will be described based on available information.
- It is anticipated that the decision-analytic model will link the intermediate outcomes derived from the remote monitoring devices to short-term costs and consequences (e.g. the impact of a change in treatment). It will then aim to link the short-term consequences to potential longer-term costs and consequences (e.g. impact of a change in disease severity to incidence of motor symptoms, falls and hip fractures) using the best available evidence.
- The cost-effectiveness of the remote monitoring devices, if feasible, will be expressed in terms of incremental cost per quality-adjusted life year and/or net health (or monetary) benefits.

2 METHODS FOR SYNTHESISING EVIDENCE OF CLINICAL EFFECTIVENESS

The systematic review will be conducted following the general principles recommended in CRD's guidance and reported in accordance with the PRISMA statement.[8]

2.1 Search strategy

Comprehensive searches of the literature will be conducted to identify all studies relating to the use of remote continuous monitoring devices (PKG, Kinesia 360, KinesiaU, PDMonitor and STAT-ON) alongside clinical judgement for monitoring motor symptoms in people with Parkinson's disease. As the literature is anticipated to be limited, all publications considering the included technologies will be sought.

An Information Specialist will design a search strategy in Ovid MEDLINE in consultation with the research team. The strategy will consist of terms for the population which will then be combined with specific interventions of interest (PKG, Kinesia 360, KinesiaU, PDMonitor and STAT-ON), and broader terms that reflect remote monitoring technologies.

The following bibliographic databases will be searched: MEDLINE(R) ALL; Embase; EconLit; APA PsycInfo; Cochrane Central Register of Controlled Trials (CENTRAL); Cochrane Database of Systematic Reviews (CDSR); Database of Abstracts of Reviews of Effects (DARE); Health Technology Assessment (HTA) Database; NHS Economic Evaluation Database (NHS EED); and the International Health Technology Assessment Database.

In addition, the following resources will be searched for ongoing, unpublished or grey literature: ClinicalTrials.gov; EU Clinical Trials Register; and the WHO International Clinical Trials Registry Platform.

An example search strategy for Ovid MEDLINE is included in Appendix 1. The final MEDLINE strategy will be adapted for use in all resources searched. There will be no restrictions by language, date, or study design; animal-only studies will be removed.

Additionally, company websites will be searched to identify relevant publications and other materials relating to the technology. The companies will be contacted to provide details of all studies (completed or ongoing) that they have conducted. Reference lists of relevant reviews and studies will be scanned to identify any additional relevant reports.

2.1.1 Additional literature searching

In order to identify and appraise existing evidence on the clinical and cost-effectiveness of remote continuous monitoring devices, and to inform the conceptualisation of a decision model, it is anticipated that sources of evidence on the clinical and cost-effectiveness of other parts of the treatment pathway will be required, beyond that reported in the literature on the technologies themselves.

Systematic database searches for additional evidence on clinical effectiveness, cost-effectiveness and quality of life data will therefore also be undertaken. The exact nature of the searches will depend on the extent of the identified literature, and what is required to assess the general clinical and economic impact of remote continuous monitoring devices.

Anticipated areas for searching include, but are not limited to:

- Evidence on levodopa treatment, and its modification
- Adverse events associated with common treatments used in Parkinson's disease
- Health-related quality of life associated with disease progression
- The association between motor symptoms, rating scale scores (such as the UDPRS, MBRS and the Hoehn and Yahr scales) and later morbidity, mortality and quality of life
- Resource use and direct health care costs associated with Parkinson's disease in the UK.

It is anticipated that a systematic literature review will be undertaken to identify studies reporting the direct health care resources utilised by patients in the UK and any studies which establish the relationship between health care costs and disease activity. The inclusion criteria for studies will be restricted to those which report data in the UK only.

Database searches will initially focus on identifying systematic reviews in these areas. If systematic reviews are not available, more specific searches to identify studies of relevance to UK practice will be undertaken.

Further, pragmatic supplementary searches for primary and secondary data (including existing systematic reviews) will be carried out as necessary, depending on the gaps and limitations identified during the review of clinical and economic evidence.

2.2 Study selection

Two reviewers will independently screen all titles and abstracts. Full papers of any records that may be relevant will be obtained where possible and independently screened by two reviewers according

to the inclusion criteria listed below. Any disagreements will be resolved through discussion and, where necessary, consultation with a third reviewer.

2.3 Inclusion criteria

Population

- People with Parkinson's disease.

Remote continuous monitoring devices may not be suitable for people with severe cognitive impairment, Alzheimer's disease or people with impulse disorders. This is because they can require user input to measure medical compliance, so may cause stress and anxiety in these patients. Devices may be unsuitable for people with some physical disabilities (such as wheelchair users), where this inhibits the wearing of, or functioning of, the device.

Interventions

Remote monitoring devices (as listed in Section 1.2) alongside clinical judgement for monitoring motor and non-motor symptoms in people with Parkinson's disease.

Comparators

Clinical judgement of disease symptoms without the use of remote monitoring devices, which may include the use of rating scales.

Outcomes

See Section 1.6 for a full list of intended outcomes.

Study designs

Due to the anticipated small number of studies and publications likely to be eligible, all study designs will be included, provided they report evidence on the outcomes listed.

2.4 Data extraction strategy

A data extraction form will be developed and piloted. Data on the intervention, patient characteristics and outcomes will be extracted by one reviewer and independently checked by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third reviewer where necessary. Where feasible, data will be electronically extracted from figures presented in publications. If time constraints allow, attempts will be made to contact authors and/or manufacturers to access trial data held in repositories, and to obtain missing data, where necessary. Data from relevant studies with multiple publications will be extracted and reported as a single study. The most recent or most

complete publication will be used in situations where we cannot exclude the possibility of overlapping populations.

2.5 Quality assessment strategy

Risk of bias in RCTs will be assessed using the latest version of the Cochrane risk of bias tool.[9] A tool for assessing the risk of bias of non-randomised studies will be developed using relevant criteria such as those outlined in CRD's guidance on undertaking systematic reviews.[10] Diagnostic accuracy studies will be assessed using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) tool[11] and comparative diagnostic accuracy studies will be assessed using the QUADAS-C (Quality Assessment of Diagnostic Accuracy Studies-Comparative) tool.[12]

Quality assessment will be performed by one reviewer and independently checked by a second reviewer. Any disagreements will be resolved through discussion and, where necessary, consultation with a third reviewer.

2.6 Methods of analysis/synthesis

In the initial synthesis, the results of data extraction will be presented in structured tables and as a narrative summary, grouped by population and intervention characteristics. Where sufficient clinically and statistically homogenous data are available, data will be pooled using appropriate meta-analytic techniques, as described below; however, it is anticipated that a narrative approach to synthesis will be required for most outcomes.

Synthesis of association outcomes

Data on the association between the output from remote monitoring and clinical rating scales will be summarised in tables and figures, where feasible. If sufficient studies report data on accuracy (sensitivity and specificity, or the data to calculate these), then bivariate meta-analyses of sensitivity and specificity will be performed.[13] If sufficient studies report correlations or regression parameters, these will be pooled using standard random-effects meta-analysis.

Synthesis of clinical outcomes and intermediate impact of monitoring

Quantitative data on short and long-term clinical outcomes will be tabulated or plotted. Where there are sufficient studies reporting the same clinical outcomes, results will be synthesised using standard random-effects meta-analyses. Where data are insufficient for meta-analysis a narrative synthesis will be performed, by comparing the tabulated results across studies to identify broad evidence of effectiveness.

Synthesis of survey and opinion data

Any quantitative data on these outcomes will be meta-analysed or synthesised narratively, as described for clinical outcomes. Qualitative evidence for these outcomes will be summarised in suitable tables. A broad thematic synthesis will be used to identify key issues arising from the extracted evidence, including key areas of agreement or disagreement across the included literature.

Investigation of heterogeneity and subgroup analyses

For clinical outcomes where meta-analyses are performed, heterogeneity will be investigated by examining forest plots, considering the I^2 statistic, and if feasible, by performing separate meta-analyses in different subgroups of studies or participants.

Additional clinical evidence

To support the development of the decision model, we expect additional reviews to be required (See Section 2.1.1 "**Error! Reference source not found.**" above).

Systematic reviews (or UK-relevant studies in the absence of reviews) will be summarised using narrative synthesis. If relevant and feasible, results from individual studies will be pooled using standard random effects meta-analysis.

2.7 Methods for estimating quality of life

Health-related quality of life associated with disease severity will be estimated. It is expected that measures of disease severity will be expressed in terms of different instruments of disease activity (e.g. UPDRS, Modified-UPDRS, MBRS, Hoehn and Yahr). In accordance with the NICE reference case, health-related quality of life utility values should be based on the EuroQoL – EQ5D instrument. Therefore, a systematic review of utility studies will be carried out to identify relevant studies which i) directly estimate EQ-5D utility values; and ii) establish the relationship between EQ-5D utility and measures of disease severity (including mapping studies).

3 METHODS FOR SYNTHESISING EVIDENCE OF COST EFFECTIVENESS

Relevant cost-effectiveness evidence on the use of remote monitoring devices (PKG, Kinesia 360, KinesiaU, PDMonitor and STAT-ON) for continuous monitoring of motor and non-motor symptoms in people with Parkinson's disease will be systematically identified, appraised for quality and narratively summarised. The aim of the review will be to examine any existing decision-analytic models used to assess the cost-effectiveness of the remote monitoring technologies against any comparator(s), in order to identify key issues and areas of uncertainty that could be addressed in the development of a new decision-analytic model to inform the cost-effectiveness of the devices in the NHS.

3.1 Identifying and systematically reviewing published cost-effectiveness studies

The results of the comprehensive literature searches carried out to identify all studies relating to the use of the remote monitoring devices (Section 2.1) will be used to identify any relevant studies of the cost-effectiveness of the technologies in people with Parkinson's disease. A broad range of studies will be considered in the assessment of cost-effectiveness including economic evaluations conducted alongside clinical trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) will be included in the review of economic literature.

The main findings of existing economic evaluations will be narratively summarised and tabulated for comparison within the text of the report. In particular, information will be extracted on the comparators, study population and setting, main analytic approaches (e.g. patient-level analysis/ decision-analytic modelling), primary outcome specified for the economic analysis, details of adjustment for quality of life, direct costs and indirect costs, estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty (e.g. deterministic/probabilistic sensitivity analysis).

The review will examine existing decision-analytic models in detail, with the aim of identifying important structural assumptions, highlighting key areas of uncertainty and outlining the potential issues of generalising from the results of existing models. This review will be used to identify the central issues associated with adapting existing decision models to address the current decision problem and assist in the development of a new decision model that addresses issues identified in the clinical and cost-effectiveness review.

In the event that the existing cost-effectiveness literature for the five devices is limited, we will undertake further targeted literature searches for cost-effectiveness studies evaluating pharmacological (e.g. levodopa, dopamine agonists) and non-pharmacological (e.g. deep brain stimulation) interventions for the management of symptoms in people with Parkinson's disease. The inputs and assumptions in these studies will be considered as part of the conceptualisation and development of a new decision model. These studies will not be subject to a formal assessment but we will describe the assumptions and data sources underpinning any linked-evidence approach that captures the link between short-term clinical outcomes (e.g. changes in symptom severity using different rating scales, time spent in 'on/off' periods) and long-term morbidity (e.g. disease severity, incidence of motor symptoms, sleeping patterns) and mortality. If the linked evidence approaches and data sources from these models are considered appropriate and relevant for the current decision problem, these studies will be used to assist in the overall development of a new decision-analytic model for the evaluation of the devices. In particular, attention will be given to identifying important parameter estimates and sources of data inputs, as well as highlighting key areas of uncertainty in linking evidence on short- and long-term outcomes in Parkinson's disease.

3.2 Development of a health economic model

Where evidence permits, a decision-analytic model will be developed to estimate the cost-effectiveness of the five remote monitoring devices as an adjunct to clinical judgement for the assessment of motor and non-motor symptoms in people with Parkinson's disease compared to clinical judgement alone. It may not be feasible to assess the cost-effectiveness of all devices compared to clinical judgement alone. In this case, the range of costs and resource consequences and potential clinical benefits associated with these devices will be described based on available information. The population, interventions and comparator are as set out in Sections 1.2, 1.3 and 1.5, while the outcomes to be considered are those reported in Section 1.6

The model will be developed in accordance with the NICE reference case. The perspective will be that of the National Health Services and Personal Social Services, health benefits will be expressed in terms of quality-adjusted life years (QALYs) and both costs and QALYs will be discounted at a rate of 3.5% per annum.

3.2.1 General structure of the model

The decision-analytic model will be designed to reflect the potential health and economic benefits of introducing the devices into current practice as an adjunct to clinical judgement for the assessment of motor and non-motor symptoms in people with Parkinson's disease. It is anticipated that short-term outcomes associated with the use of the monitoring devices will be modelled with a decision tree structure, which reflects the impact of the devices on initial and intermediate outcomes (such as

UDPRS, MBRS and Hoehn and Yahr rating scale scores, frequency and length of clinical and/or remote appointments, impact on clinical decision making, including change in treatment) compared to the expected corresponding outcomes based on clinical judgement alone. Where possible, the model will be populated using results from the clinical effectiveness review (Section 1.6.2).

As a result of changes in intermediate outcomes, with and without remote monitoring, consideration will then be given to potential longer-term impacts on clinical outcomes and subsequent prognosis over a patient's lifetime. While consideration will be given to all the clinical outcomes listed in Section 1.6.3, the longer-term outcomes are expected to include any impact on disease severity and progression of symptoms (motor and non-motor), adverse effects of treatment, hospitalisations, and mortality. Where data permits, we will aim to use the best available evidence to quantify the link between the intermediate and clinical outcomes. Further literature searches may be required to inform the linked-evidence approach.

Depending on data availability, alternative modelling approaches may be explored to assess the impact of improved treatment decisions on costs, patient and carer health-related quality of life, and cost-effectiveness. For example, if feasible, the model may (i) track the consequences of improved symptom management that results from changes in clinical decision-making associated with the remote monitoring devices; or (ii) track the disease severity as measured by change in UPDRS (or alternative rating scales) score associated with the remote monitoring devices. The report will include a full description of the modelled approach(es) used, including an assessment of the modelling assumptions required to inform the approach(es).

The model will be populated using results from the systematic clinical effectiveness review, other focused reviews to inform key parameters (e.g. health-related quality of life utility values), routine sources of cost data, and if necessary additional study specific cost estimates provided by experts and/or relevant investigators.

3.3 Evaluation of costs and cost effectiveness

The resource utilisation and costs associated with current clinical management of Parkinson's disease, with and without the remote monitoring devices, are expected to include those listed in Section 1.6.5. Data for the cost analysis will be obtained from routine NHS sources, published studies and information provided by the manufacturers of the devices.

The cost-effectiveness of the remote monitoring devices will be compared to current standard clinical practice for the assessment of motor and non-motor symptoms in people with Parkinson's disease. In the case where this is not feasible due to a lack of comparative effectiveness evidence for some of the devices compared to clinical judgement alone, the range of costs and resource consequences and

potential clinical benefits associated with these devices will be described based on available information.

The specific objectives of the cost-effectiveness analysis are:

- To structure an appropriate decision model to characterise existing care pathways and the subsequent impact of introducing remote monitoring devices into standard clinical practice for people with Parkinson's disease.

- To populate the model using the most appropriate data, identified systematically from published literature, routine data sources and potentially using data elicited from relevant clinical experts and manufacturers.

- To relate intermediate outcome measures associated with remote monitoring to subsequent treatment decisions and/or disease-status to final health outcomes, where feasible based on the available evidence. Final health outcomes will be evaluated in terms of QALYs. This is necessary in order to provide decision makers with an indication of the health gain achieved by each intervention, relative to their additional cost, in units which permit comparison with other uses of health service resources.

- To estimate the incremental cost-effectiveness of the devices compared with standard clinical practice alone, for people with Parkinson's disease, based on an assessment of the long-term NHS and Personal Social Service costs and QALYs. The time horizon of the model will be sufficient to capture both the short-term and longer-term outcomes. The final specification of the model will be determined during the review and model conceptualisation stage.

- To characterise the uncertainty in the data used to populate the model and to present the resulting uncertainty in the results to decision makers. A probabilistic model will be developed which requires that, where possible, uncertainty in inputs are reflected through the use of appropriate probability distributions, rather than as a fixed parameter input. Using Monte Carlo simulation, this parameter uncertainty will be translated into uncertainty in the overall results. This will be presented graphically using cost-effectiveness acceptability curves, which show the probability that an intervention is expected to be cost-effective for a given estimate of health opportunity costs (cost-effectiveness threshold).

- To undertake sensitivity, scenario and/or threshold analysis to explore the robustness of the cost-effectiveness results to changes in the parameter inputs (e.g. impact of alternative monitoring schedules), structural assumptions of the model and the time horizon.

It is anticipated that the model will be developed in Microsoft Excel.

4 HANDLING INFORMATION FROM THE COMPANIES

The EAG will consider any data or evidence supplied by the companies involved. If the data meet the inclusion criteria for the review they will be extracted, quality assessed and synthesised in accordance with the procedures outlined in this protocol. It may not be possible to include data received later than 30 April 2022.

Any 'commercial in confidence' data provided by a company and specified as such will be highlighted in blue and underlined in the assessment report. Any 'academic in confidence' data provided by the manufacturers or study analysts will be highlighted in yellow and underlined in the assessment report. Confidential data will be stored securely, and will only be accessible to members of the project team.

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.

5 COMPETING INTERESTS OF AUTHORS

None of the authors have any conflicts of interest.

6 TIMETABLE/MILESTONES

Milestone	**Date to be completed**
Submission of final protocol	17 February 2022
Submission of progress report	6 May 2022
Submission of draft Diagnostic Assessment Report	5 July 2022
Submission of final Diagnostic Assessment Report	2 August 2022

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Appendix 1: MEDLINE search strategy

Database: Ovid MEDLINE(R) ALL <1946 to January 31, 2022>

Search Strategy:

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1 Parkinson Disease/ (74617)

2 (parkinson* adj2 (disease* or syndrom* or disorder* or complex)).ti,ab,kw. (111790)

3 or/1-2 (124681)

4 Wearable Electronic Devices/ (5431)

5 Telemetry/ (10052)

6 Remote Sensing Technology/ (3551)

7 ((continuous* or remote*) adj2 (measure* or monitor* or sensor*)).ti,ab,kw. (50230)

8 (((wear* or worn or wrist* or ankle* or body* or waist* or belt*) adj2 (tech* or device* or sensor*)) and (remote* or continuous*)).ti,ab,kw. (2412)

9 (((inertia* or kinetic* or motor or gait or bradykine* or dyskine* or tremor* or shaking or instability or stability or balance or sleep*) adj2 (tech* or device* or sensor*)) and (remote* or continuous*)).ti,ab,kw. (1523)

10 telemetr*.ti,ab,kw. (9720)

11 ((smart watch* or smart-watch* or smartwatch*) and (remote* or continuous*)).ti,ab,kw. (171)

12 (((mobile adj (health* or app*)) or (e-health or eHealth or m-health or mHealth)) and (remote* or continuous*)).ti,ab,kw. (2230)

13 ((remote* or continuous*) and ((ambulatory or outpatient* or patient* or physiologic*) adj2 (monitor* or manage*))).ti,ab,kw. (8954)

14 or/4-13 (81597)

15 3 and 14 (633)

16 KinetiGraph*.ti,ab,kw,rn. (33)

17 (PKG* not "protein kinase").ti,ab,kw,rn. (1002)

18 (kineti* adj graph*).ti,ab,kw,rn. (76)

19 Kinesia*.ti,ab,kw,rn. (102)

20 (STAT ON* or STAT-ON*).ti,ab,kw,rn. (30)

21 (PDMonitor* or (PD adj monitor*)).ti,ab,kw,rn. (37)

22 or/16-21 (1251)

23 3 and 22 (101)

24 15 or 23 (713)

25 exp animals/ not humans/ (4951717)

26 24 not 25 (688)

27 remove duplicates from 26 (687)

Key:

/ = subject heading (MeSH heading)

* = truncation

ti,ab,kw = terms in title, abstract, or keyword fields

rn = search of registry number field

adj2 = terms within three words of each other (any order)